Fredericamycin derivatives

The invention relates to novel fredericamycin derivatives, to drugs containing said derivatives or the salts thereof, and to the use of the fredericamycin derivatives for treating diseases, particularly cancer diseases.

Fredericamycin has been isolated 1981 from *Streptomyces griseus,* and demonstrates anti-cancer activity.

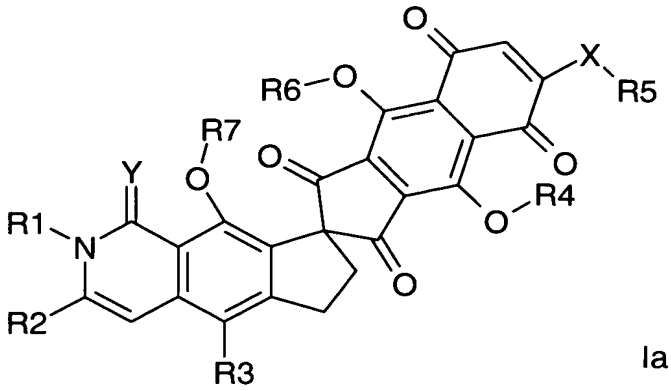
Fredericamycin and several fredericamycin derivatives are known.

In Heterocycles 37 (1994) 1893 – 1912, J. Am. Chem. Soc. 116 (1994) 9921 – 9926, J. Am. Chem. Soc. 116 (1994) 11275 – 11286, J. Am. Chem. Soc. 117 (1995) 11839 – 11849, JP 2000-072752, and in J. Am. Chem. Soc. 123 (2001), various total syntheses of fredericamycin A have been described, some being enantio-selective.

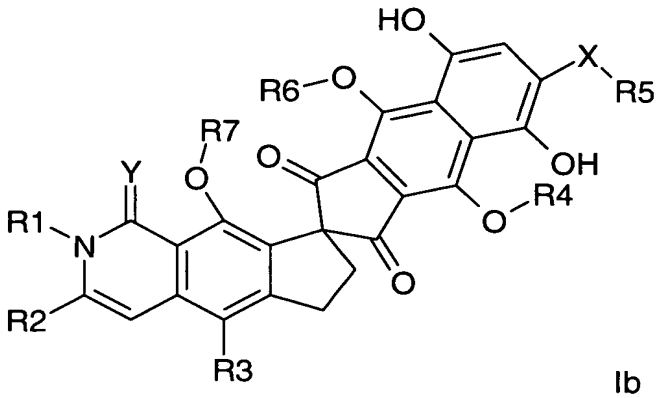
In US 4673768, alkali salts of the fredericamycin A are described. In US 4584377, fredericamycin derivatives are described, particularly derivatives acylated in ring E and F. In US 5,166,208, fredericamycin derivatives are described as well, particularly derivatives carrying thio and amino substituents in ring F. The derivatives are generated semi-synthetically or fully synthetically.

Surprisingly it was found that fredericamycin derivatives, especially those derivatized in ring A, represent potent drugs. Also, a possibility was found to introduce such residues in ring A semi-synthetically, with which the water solubility and/or the biological effect, the spectrum of action in comparison with fredericamycin, can be significantly increased. Furthermore, an alternative method was found to make fredericamycin and its derivatives water-soluble by generating cyclodextrin inclusion compounds.

The invention relates to novel fredericamycin derivatives with the general Formula Ia or Ib:



Ia

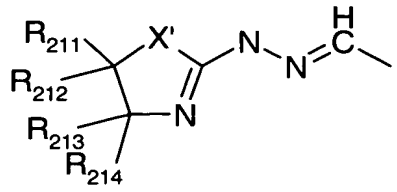


Ib

wherein in each,

R1 means H, C_1-C_6 alkyl, cycloalkyl, C_1-C_4 alkylcycloalkyl,

R2 means H, C_1-C_{14} alkyl, C_2-C_{14} alkenyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkyl heteroaryl, C_2-C_4 alkenylheteroaryl, cycloalkyl, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y = independently selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH, SR21), $(CH_2)_rCH_2NHCOR21$, $(CH_2)_rCH_2OCOR21$, $(CH_2)_rCH_2NHCSR21$, $(CH_2)_rCH_2S(O)nR21$, with n = 0, 1, 2, $(CH_2)_rCH_2SCOR21$, $(CH_2)_rCH_2OSO_2$-R21, $(CH_2)_rCHO$, $(CH_2)_rCH=NOH$, $(CH_2)_rCH(OH)R21$, -$(CH_2)_rCH=NOR21$, $(CH_2)_rCH=NOCOR21$, $(CH_2)_rCH=NOCH_2CONR21R22$, $(CH_2)_rCH=NOCH(CH_3)CONR21R22$, -$(CH_2)_rCH=NOC(CH_3)_2CONR21R22$, $(CH_2)_rCH=N$-NHCO-R23, $(CH_2)_rCH=N$-NHC(O)NH-R23, $(CH_2)_rCH=N$-NHC(S)NH-R23, $(CH_2)_rCH=N$-NHC(NH)NH-R23, $(CH_2)_rCH=N$-NHC(NH)-R23, $(CH_2)_rCH=N$-NHCO-CH_2NHCOR21, $(CH_2)_rCH=N$-O-CH_2NHCOR21, $(CH_2)_rCH=N$—NHCS-R23, $(CH_2)_rCH=CR24R25$ (trans or cis), $(CH_2)_rCOOH$, $(CH_2)_rCOOR21$, $(CH_2)_rCONR21R22$, -$(CH_2)_rCH=NR21$, $(CH_2)_rCH=N$-NR21R22,



, and the $(CH_2)_r$-chain elongated residue $(CH_2)_rCH=N-N-(C_3NX'R211R212R213R214)$ (with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently H or C_1-C_6 alkyl), $-(CH_2)_rCH=N-NHSO_2$ aryl, $-(CH_2)_rCH=N-NHSO_2$ heteroaryl, with r = 0, 1, 2, 3, 4, 5, preferably 0,

R21, R22 are independently H, C_1-C_{14} alkyl, C_1-C_{14} alkanoyl, C_1-C_6 alkylhydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylamino, C_1-C_6 alkylamino-C_1-C_6 alkyl, C_1-C_6 alkylamino-di-C_1-C_6 alkyl, cycloalkyl, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, aryl, aryloyl, C_1-C_4 alkylaryl, heteroaryl, heteroaryloyl, C_1-C_4 alkylheteroaryl, cycloalkanoyl, C_1-C_4 alkanoylcycloalkyl, heterocycloalkanoyl, C_1-C_4 alkanoylheterocycloalkyl, C_1-C_4 alkanoylaryl, C_1-C_4 alkanoylheteroaryl, mono- and di-sugar residues linked through a C atom which would carry an OH residue in the sugar, wherein the sugars are independently selected from the group consisting of glucuronic acid and its stereo isomers at all optical atoms, aldopentoses, aldohexoses, including their desoxy compounds (as e.g. glucose, desoxyglucose, ribose, desoxyribose), or R21 and R22, together with the N, form a ring with 4, 5, 6, 7, or 8 members, which may optionally contain still another heteroatom selected from the group N, O, S,

R23 independently of R21, has the same meanings as R21, or CH_2-pyridinium salts, CH_2-tri-C_1-C_6 alkylammonium salts, $CONH_2$, $CSNH_2$, CN, CH_2CN,

R24 independently of R21, has the same meanings as R21, or H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, NHCOR21,

R25 independently of R21, has the same meanings as R21, or H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, NHCOR21,

R24, R25 together with the N, form a ring with 4, 5, 6, 7, or 8 members, which may optionally contain still another heteroatom selected from the group N, O, S,

R3 means H, F, Cl, Br, I, OH, OR31, NO_2, NH_2, NHR31, NR31R32, NHCHO, NHCOR31, $NHCOCF_3$, $CH_{3-m}hal_m$ (with hal = Cl, F, particularly F, and m = 1, 2, 3), OCOR31,

R31, R32 are independently C_1-C_6 alkyl, or R31 and R32, together with the N, form a ring with 4, 5, 6, 7, or 8 members, which may optionally contain still another heteroatom selected from the group N, O, S,

R5 means H, C_1-C_{20} alkyl, cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{10} alkinyl, C_1-C_4 alkyl cycloalkyl, heterocycloalkyl, C_1-C_4 alkyl heterocycloalkyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl, $C_mH_{2m+o-p}Y_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y = independently selected from the group consisting of halogen, OH, OR51, NH_2, NHR51, NR51R52, SH, SR21), $(CH_2)_sCH_2NHCOR51$, $(CH_2)_sCH_2NHCSR51$, $(CH_2)_sCH_2S(O)nR51$, with n = 0, 1, 2, $(CH_2)_sCH_2SCOR51$, $(CH_2)_sCH_2OCOR51$, $(CH_2)_sCH_2OSO_2$-R51, $(CH_2)_sCH(OH)R51$, $(CH_2)_sCOOH$, $(CH_2)_sCOOR51$, $(CH_2)_sCONR51R52$, with s = 0, 1, 2, 3, 4, 5, preferably 0, mono- and di-sugar residues linked through a C atom which would carry an OH residue in the sugar, wherein the sugars are independently selected from the group consisting of glucuronic acid and its stereo isomers at all optical atoms, aldopentoses, aldohexoses, including their desoxy compounds (as e.g. glucose, desoxyglucose, ribose, desoxyribose), with the mono-sugar residues such as aldopentoses, aldohexoses, including their desoxy compounds (as e.g. glucose, desoxyglucose, ribose, desoxyribose) being preferred, with R51, R52 which are capable of independently adopting the meaning of R21, R22,

R4, R6, R7 independently mean H, C_1-C_6 alkyl, CO-R41,

R41 independently from R21, has the same meanings as R21,

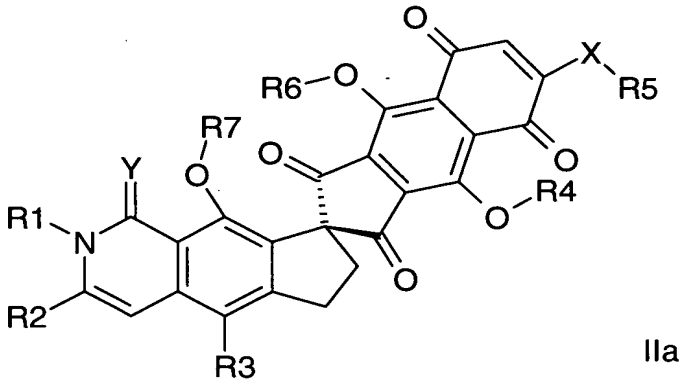
X means O, S, NH, N-R8, wherein R8 independently from R5 may adopt the same meaning as R5, or R5 and R8, together with the N, form a ring with 4, 5, 6, 7, or 8 members, which may optionally contain still another heteroatom selected from the group N, O, S,

or X-R5 may together be H,

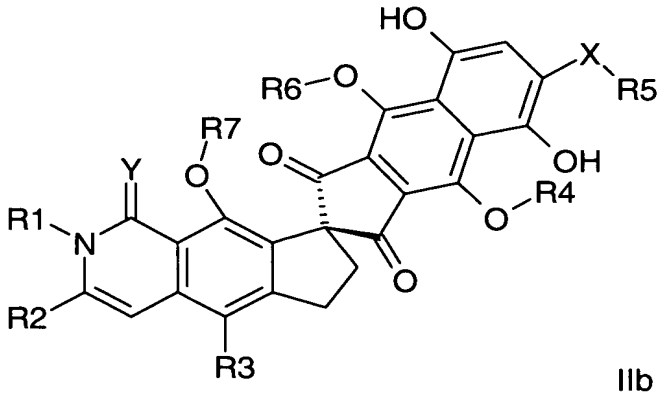
Y means O, S, NR9, wherein R9 may be H or C_1-C_6 alkyl,

as well their stereoisomers, tautomers, and their physiologically tolerable salts or inclusion compounds, wherein the residues for Formula Ia may not concomitantly adopt the following meaning, except in case of cyclodextrin inclusion compounds: R1: H, C_1-C_6 alkyl, R2: C_1-C_6 alkyl, C_2-C_6 alkenyl, R3: H, R4 and R6 identical, and independently H, C_1-C_6 alkyl, CO-R41, with R41 being C_1-C_6 alkyl, aryl, and R7 being H, C_1-C_6 alkyl, Y: O, and for Formula Ib: R1: H, R2: pentyl, 1-pentenyl, 3-pentenyl, 1,3-pentdienyl, R3: H, R4 and R6 being H, and X-R5 being methoxy, Y: O. Preferably, the substituents do not concomitantly adopt the following meaning: R1, R3: H, R2: H, alkyl, hydroxyalkyl, particularly monohydroxyalkyl, alkoxyalkyl, CF_3, $(CH_2)_rCOOH$, CHO, $CONH_2$, $(CH_2)_rCH_2NHCO$ alkyl, $(CH_2)_rCH_2OCO$ alkyl, $(CH_2)_rCH_2NHCS$ alkyl, CH=NOH, CH=NO alkyl, aryl, alkylaryl, alkylheteroaryl, alkenyl, hydroxyalkenyl, particularly monohydroxyalkenyl, R4, R6, R7: H, alkyl, X-R5: H, R5: H, alkyl, aryl.

Preferred are compounds of Formula IIa or IIb



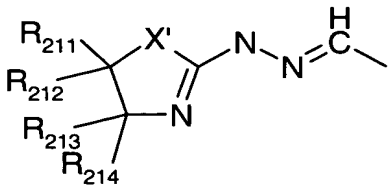
IIa



IIb

wherein the meaning of the residues R1-R41, X is as described above, their tautomers and their physiologically tolerable salts or inclusion compounds, wherein the residues for Formula Ia may not concomitantly adopt the following meaning, except in the case of cyclodextrin inclusion compounds: R1: H, C_1-C_6 alkyl, R2: C_1-C_6 alkyl, C_2-C_6 alkenyl, R3: H, R4 and R6 identical, and independently H, C_1-C_6 alkyl, CO-R41, with R41 being C_1-C_6 alkyl, aryl, and R7 being H, C_1-C_6 alkyl, Y: O, and for Formula Ib: R1: H, R2: pentyl, 1-pentenyl, 3-pentenyl, 1,3-pentdienyl, R3: H, R4 and R6 being H, and X-R5 being methoxy, Y: O.

The invention further relates to compounds of Formula Ia, Ib, IIa or IIb, in which the residues R, except for R2, have the above described meanings, and the water solubility of R2 is at least two times higher, preferably at least five timer higher, more preferred at least ten times higher, especially preferred at least fifty time higher, particularly one hundred times higher, or even five hundred times higher than of R2 being CH=CH-CH=CH-CH_3, when all other residues are maintained. The increase in the water solubility is achieved e.g. by introduction of groups which can form additional hydrogen bonds, and/or are polar, and/or are ionic. A key intermediate are compounds with an aldehyde function in R2.

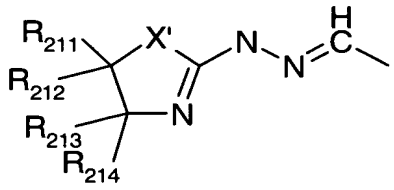
For R2 preferred is also the group of the residues $C_mH_{2m+o-p}Y_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y = independently selected from the group of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH, SR21), $(CH_2)_rCH_2NHCOR21$, $(CH_2)_rCH_2OCOR21$, $(CH_2)_rCH_2NHCSR21$, $(CH_2)_rCH_2S(O)nR21$, with n = 0, 1, 2, $(CH_2)_rCH_2SCOR21$, $(CH_2)_rCH_2OSO_2$-R21, $(CH_2)_rCH(OH)R21$, $(CH_2)_rCOOH$, $(CH_2)_rCOOR21$, $(CH_2)_rCONR21R22$. Still particularly preferred is the group of the aldehyde-derived residues $(CH_2)_rCHO$, $(CH_2)_rCH=NOH$, -$(CH_2)_rCH=NOR21$, $(CH_2)_rCH=NOCOR21$, $(CH_2)_rCH=NOCH_2CONR21R22$, $(CH_2)_rCH=N$-NHCO-R23, $(CH_2)_rCH=N$-NHC(O)NH-R23, $(CH_2)_rCH=N$-NHC(S)NH-R23, $(CH_2)_rCH=N$-NHC(NH)NH-R23, $(CH_2)_rCH=N$-NHC(NH)-R23, $(CH_2)_rCH=N$-NHCO-CH_2NHCOR21, $(CH_2)_rCH=N$-O-CH_2NHCOR21, $(CH_2)_rCH=N$—NHCS-R23, $(CH_2)_rCH=CR24R25$ (trans or cis), $(CH_2)_rCH=NR21$, $(CH_2)_rCH=N$-NR21R22, 

,and the $(CH_2)_r$-chain elongated residue $(CH_2)_rCH=N$-N-($C_3NX'R211R212R213R214$) (with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently H or C_1-C_6 alkyl), -

$(CH_2)_rCH=N-NHSO_2$ aryl, $(CH_2)_rCH=N-NHSO_2$ heteroaryl, $(CH_2)_rCH=CH$ heteroaryl, with r = 0, 1, 2, 3, 4, 5, preferably 0.

From the aldehydes and thereof derived compounds, such are preferred in which at least R1 or r3 are not H, if R4 to R7 are H or alkyl.

Preferred residues in R2 are further heteroaryl, cycloaryl, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkyl heterocycloalkyl, $C_mH_{2m+o-p}Y_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y = independently selected from the group of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH, SR21), $CH_2NHCOR21$, $CH_2NHCSR21$, $CH_2S(O)nR21$, with n = 0, 1, 2, $CH_2SCOR21$, CH_2OSO_2-R21, CH(OH)R21, CH=NOCOR21, -$CH=NOCH_2CONR21R22$, -$CH=NOCH(CH_3)$-CONR21R22, $CH=NOC(CH_3)_2CONR11R22$, CH=N-NHCO-R23, -$CH=N-NHCO-CH_2NHCOR21$, $CH=N-O-CH_2NHCOR21$, -CH=N-NHCS-R23, CH=CR24R25 (trans or cis), CONR21R22, -CH=NR21, -CH=N-NR21R22,



, (with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently H or C_1-C_6 alkyl), $CH=N-NHSO_2$ aryl, $H=N-NHSO_2$ heteroaryl.

Furthermore, compounds as described above are preferred, in which R3 means F, Cl, Br, I, OH, OR31, NO_2, NH_2, NHR31, NR31R32, NHCHO, NHCOR31, $NHCOCF_3$, $CH_{3-m}hal_m$ (with hal = Cl, F, particularly F, and m = 1, 2, 3), OCOR31, with the above described meanings for R31, R32.

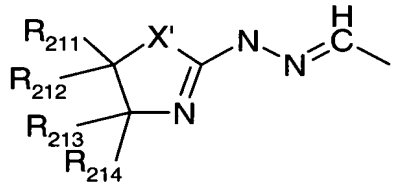
Also preferred are compounds as described above, in which X means N or S, especially when R3 is H or halogen, and/or R2 is alkenyl, particularly butadienyl or 1, 3-pentdienyl.

Also preferred are compounds as described above, in which X-R5 is OH, and particularly their salts, and preferred in compounds of Formula Ia or IIa, since this acidic OH group may easily be deprotonized, which increases the water solubility and/or the biological efficacy.

Furthermore preferred are still compounds as described above, wherein the residues R preferably independently adopt one or more of the following meanings:

R1 means H, C_1-C_5 alkyl, cycloalkyl, especially H,

R2 means C_1-C_5 alkyl, C_1-C_4 alkylaryl, C_2-C_5 alkenyl, heteroaryl, C_1-C_4 alkylheteroaryl, C_2-C_4 alkenylheteraryl, CHF_2, CF_3, polyol side chain, particularly CHOH-CHOH-CHOH-CHOH-CH_3, CHOH-CHOH-CH=CH-CH_3, CH=CH-CHOH-CHOH-CH_3, CH_2Y (Y = F, Cl, Br, I), CH_2NH_2, $CH_2NR21R22$, $CH_2NHCOR23$, $CH_2NHCSR23$, CH_2SH, $CH_2S(O)nR21$, with n = 0, 1, 2, $CH_2SCOR21$, particularly CH_2OH, CH_2OR21, CH_2OSO_2-R21, particularly CHO, $CH(OR21)_2$, $CH(SR21)_2$, CN, CH=NOH, CH=NOR21, CH=NOCOR21, CH=N-NHCO-R32, CH=CR24, R25 (trans or cis), particularly COOH (particularly their physiologically tolerable salts), COOR21, CONR21R22, -CH=NR21, -CH=N-NR21R22,



, (with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently H or C_1-C_6 alkyl), -CH=N-$NHSO_2$ aryl, -CH=N-$NHSO_2$ heteroaryl, CH=N-NHCO-R23,

R21, R22 independently mean C_1-C_6 alkyl, cycloalkyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl,

R23 independently of R21, has the same meanings as R21, or CH_2-pyridinium salts, CH_2-tri-C_1-C_6 alkylammonium salts,

R24 independently of R21, has the same meanings as R21, or H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, NHCOR21,

R25 independently of R21, has the same meanings as R21, or H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, NHCOR21,

R24, R25 together mean C_4-C_8 cycloalkyl,

R3 means F, Cl, Br, I, NO_2, NH_2, NHCOR31,

R31 independently means C_1-C_6 alkyl,

R5 means H, C_1-C_6 alkyl, particularly C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, C_1-C_6 alkenyl, C_1-C_6 alkinyls, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl, $C_mH_{2m+o-p}Y_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y = independently selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH, SR21), particularly preferred is hydroxyalkyl with one or more OH groups,

R4, R6, R7 independently means H, C_1-C_5 alkyl, CO-R41,

R41 independently from R21, has the same meanings as R21,

X means O, S, NH, N-R8,

Y means O, S, NH,

as well their stereoisomers, tautomers, and their physiologically tolerable salts or inclusion compounds, wherein the residues for Formula Ia may not concomitantly adopt the following meaning, except in case of cyclodextrin inclusion compounds: R1: H, C_1-C_6 alkyl, R2: C_1-C_6 alkyl, C_2-C_6 alkenyl, R3: H, R4 and R6 are identical, and independently are H, C_1-C_6 alkyl, CO-R41, with R41 being C_1-C_6 alkyl, aryl, and R7 being H, C_1-C_6 alkyl, and for Formula Ib: R1: H, R2: pentyl, 1-pentenyl, 3-pentenyl, 1,3-pentdienyl, R3: H, R4 and R6 being H, and X-R5 being methoxy.

O, S, particularly O, are preferred for Y.

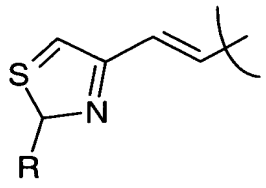
O, NH, N-R8 are preferred for X.

H, methyl, ethyl, propyl, particularly methyl, are preferred for R5.

H, methyl, ethyl, propyl, particularly methyl, are preferred for R8.

OCH_3, NH_2, $N(CH_3)_2$ are preferred for XR5.

For R2 also preferred is the residue $-CHOHCHOHCHOHCHOHCH_3$.

Furthermore, the following residues are preferred for R2: -CHCH-2-methyl-4-thiazyl, particularly 

, wherein R particularly is alkyl or NHCO alkyl, CH=NOR21, with R21 being methyl, ethyl, n-propyl, isopropyl, n-butyl, n-hexyl, benzyl, halogen benzyl, particularly fluorobenzyl and chlorobenzyl, $-CH_2CH_2$ morpholinyl.

Especially preferred are the compounds, the stereo isomers, tautomers, and physiologically tolerable salts or inclusion compounds of which, selected from the group consisting of the compounds of the examples and the compounds, demonstrate combinations of the various substituents of the examples.

Particularly preferred for R3 is H, F, Cl, Br, J, particularly F, Cl, Br, J.

Particularly preferred for R2 is C_1-C_8 alkyl, C_2-C_8 alkenyl, CH=NOR1, with R21 being C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl or heteroaryl, C_1-C_2 alkylaryl, particularly benzyl, C_1-C_2 alkylheteroaryl, wherein aryl or heteroaryl in particular have only one ring system which may be substituted once or twice with a substituent such as halogen, methyl, CF_3, OH, OMe.

Particularly preferred are derivatives of fredericamycin A in which only the above indicated, particularly preferred meanings of R2 and/or R3 are realized.

The invention furthermore relates to drugs containing the above compounds of Formula I or II together with the usual carriers and adjuvants.

Also preferred are the above mentioned drugs in combination with other agents for cancer treatment.

These compounds according to the invention are used for preparation of drugs for treatment of cancers, particularly such that may be treated by inhibition of the topoisomerases I and/or II. Cancers that can be treated with the substances according to the invention are e.g. leukemia, lung cancer, melanomas, uterus tumors, prostate tumors and colon tumors.

Also, fredericamycin A and its derivatives act against an unknown target in the cell cycle leading to apoptosis in tumor cells.

Furthermore, the compounds according to the invention, and compounds which have concomitantly adopted the following meanings in Formula Ia: R1: H, C_1-C_6 alkyl, R2: C_1-C_6 alkyl, C_2-C_6 alkenyl, R3: H, R4 and R6 identically and independently H, C_1-C_6 alkyl, CO-R41, with R41 being C_1-C_6 alkyl, aryl, and R7 being H, C_1-C_6 alkyl, and in Formula Ib: R1: H, R2: pentyl, 1-pentenyl, 3-pentenyl, 1,3-pentdienyl, R3: H, R4 and R6 being H and X-R5 being methoxy, are used for preparation of drugs for treatment of neurodermitis, parasites and for immunosuppression.

The invention also relates to a method for preparation of fredericamycin derivatives in which R2 as intermediate is $-CHOHCHOHCHOHCHOHCH_3$. These compounds are preferably transformed into aldehydes for further derivatization.

In the description and the claims, the substituents are described by the following definitions:

The term "alkyl" by itself or as part of another substituent means a linear or branched alkyl chain radical of the respectively indicated length, in which optionally a CH_2 group may be substituted by a carbonyl function. Thus, C_{1-4} alkyl may be methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl, 2-butyl, C_{1-6} alkyl, e.g. C_{1-4} alkyl, pentyl, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl, or 3,3-dimethylbutyl.

The term "C_1-C_6 alkylhydroxy" by itself or as part of another substituent means a linear or branched alkyl chain radical of the respectively indicated length which may be saturated or unsaturated, and which carries an OH group, e.g. hydroxymethyl, hydroxymethyl, 1-hydroxypropyl, 2-hydroxypropyl.

The term "alkenyl" by itself or as part of another substituent means a linear or branched alkyl chain radical with one or more C=C double bonds of the respectively indicated length, several double bonds being preferably conjugated. Thus, C_{2-6} alkenyl may for example be ethenyl, 1-propenyl, 2-propenyl, 2-methyl-2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 1,3-butdienyl, 2,4-butdienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1,3-pentdienyl, 2,4-pentdienyl, 1,4-pentdienyl, 1-hexenyl, 2-hexenyl, 1,3-hediexyl, 4-methyl-1-pentenyl, or 3,3-dimethylbutenyl.

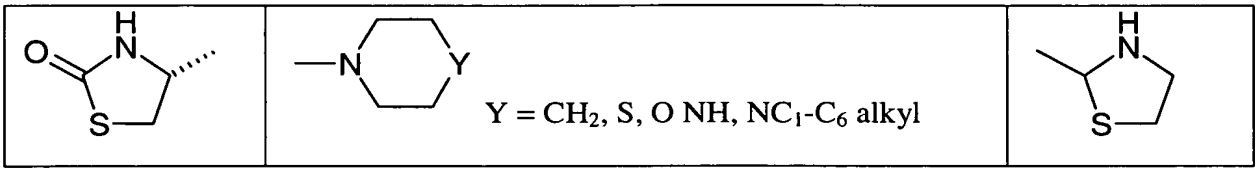
The term "alkinyl" by itself or as part of another substituent means a linear or branched alkyl chain radical with one or more C-C triple bonds of the respectively indicated length. Thus, C_{2-6} alkinyl may for example be ethinyl, 1-propinyl, 2-propinyl, 2-methyl-2-propinyl, 2-methyl-1-propinyl, 1-butinyl, 2-butinyl, 1,3-butdiinyl, 2,4-butdiinyl, 1-pentinyl, 2-pentinyl, 3-pentinyl, 1-hexinyl, 2-hexinyl, 4-methyl-1-pentinyl, or 3,3-dimethylbutinyl.

The term "halogen" stands for fluorine, chlorine, bromine, iodine, preferably bromine and chlorine.

The term "NR21R22" preferably stands for a dialkylamino group, wherein the two alkyl groups together with the N can form a ring with 5 or 6 members with optionally one more heteroatom N or O.

The term "cycloalkyl" by itself or as part of another Substituent comprises unsaturated (mono or poly, preferably mono) or saturated, cyclic carbohydrate groups with 3 to 10 C atoms, preferably 3 to 8 C atoms, such as e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohex-2-enyl, cyclohex-3-enyl, cyclohex-2,4-dienyl, 4-methylcyclohexyl, 3-methylcyclohexyl, cycloheptyl or cyclooctyl. Saturated cycloalkyls are preferred. The cycloalkyls may be substituted with up to 3 substituents, preferably with up to 1 substituent, wherein the substituents independently can have the meaning C_1-C_6 alkyl, OH, NO_2, CN, CF_3, OR11, SH, SR11, C_1-C_6 alkylhydroxy, C_1-C_6 alkyl-OR11, COOH, COOR11, NH_2, NHR11, NR11R12, halogen, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 heteroalkylaryl, wherein the residues R11 und R12 independently can mean C_1-C_{10} alkyl, cycloalkyl, C_1-C_4 alkylcycloalkyl.

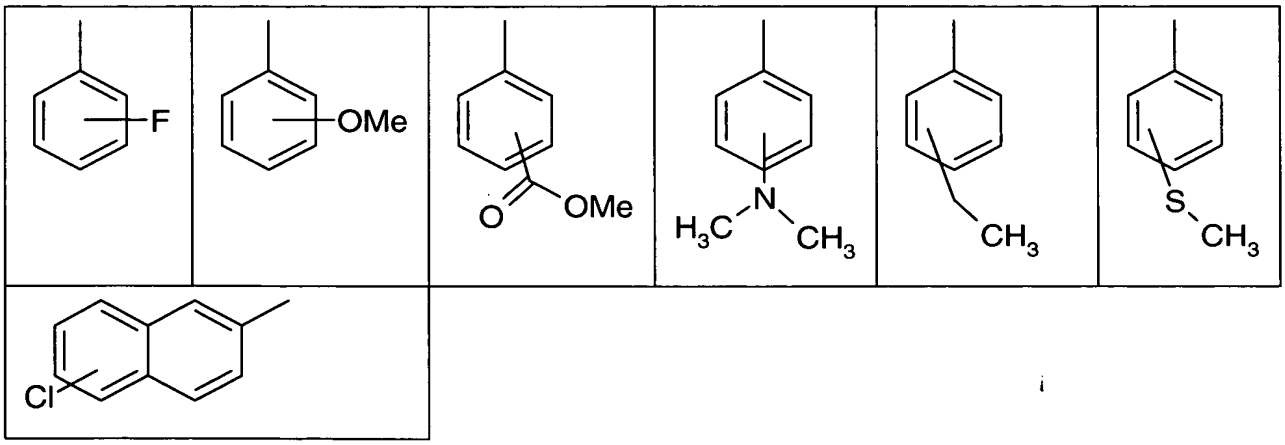
The term "heterocycloalkyl" by itself or as part of another substituent includes cycloalkyl groups, wherein up to two CH_2 groups may be substituted by oxygen, sulfur or nitrogen atoms, and one or two other CH_2 groups may be substituted by one or two carbonyl function(s), carbothionyl function(s), or a carbonyl function and a carbothionyl function, for example pyrrolidine, piperidine, morpholine or



The heterocycloalkyls may be substituted as with the cycloalkyls.

The term "aryl" by itself or as part of another substituent includes aromatic ring systems with up to 3 rings, in which at least 1 ring system is aromatic, and those with up to 3 substituents, preferably up to 1 substituent, wherein the substituents independently can have the meaning C_1-C_6 alkyl, OH, NO_2, CN, CF_3, OR11, SH, SR11, C_1-C_6 alkylhydroxy, C_1-C_6 alkyl-OR11, COOH, COOR11, NH_2, NHR11, NR11R12, halogen, wherein the residues R11 und R12 independently can mean C_1-C_{10} alkyl, cycloalkyl, C_1-C_4 alkylcycloalkyl, or R11 and R12, together with the N, form a ring with 4, 5, 6, 7 or 8 members optionally containing still another heteroatom selected from the group N, O, S.

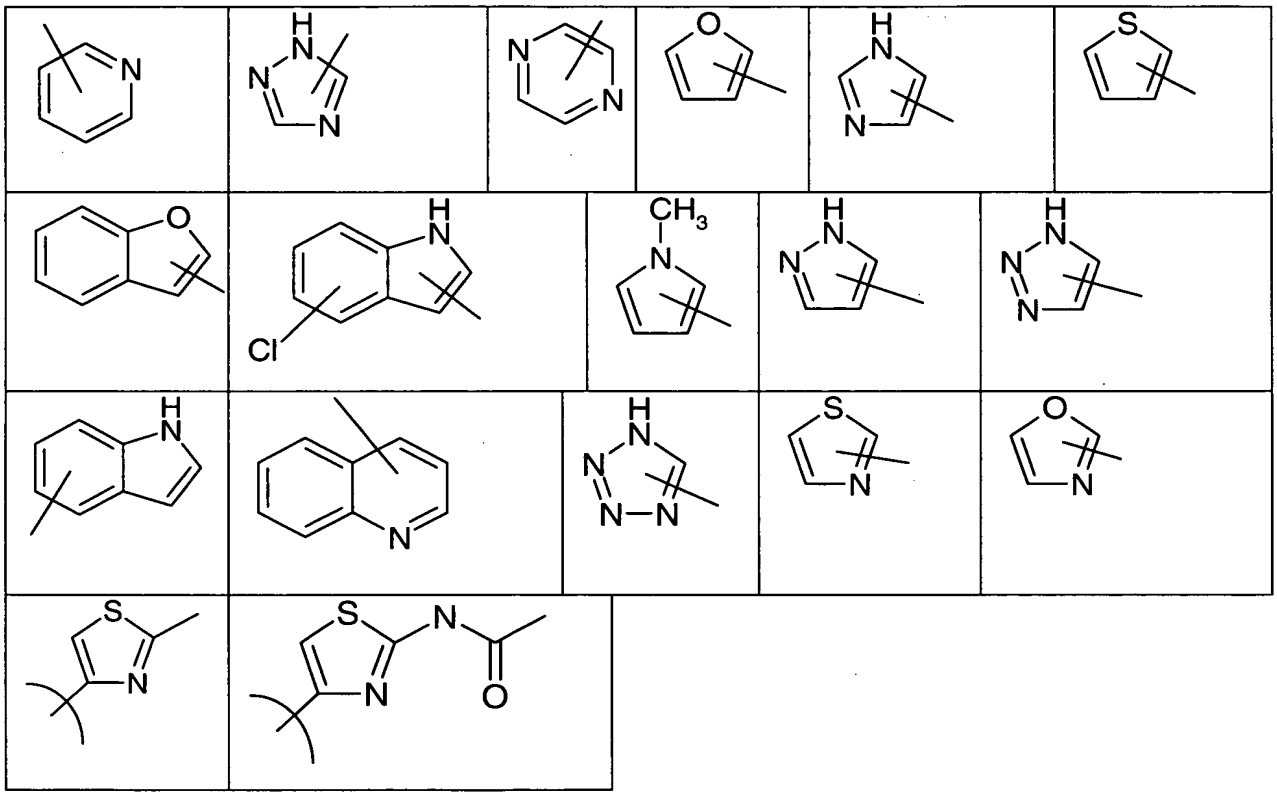
Apart from phenyl and 1-naphthyl and 2-naphthyl, preferred aryls are:



The term "heteroaryl" by itself or as part of another substituent includes aromatic ring systems with up to 3 rings and with up to 3 identical or different heteroatoms N, S, O, in

which at least 1 ring system is aromatic, and those with up to 3 substituents, preferably up to 1 substituent, wherein the substituents independently can have the meaning C_1-C_6 alkyl, OH, NO_2, CN, CF_3, OR11, SH, SR11, C_1-C_6 alkylhydroxy, C_1-C_6 alkyl-OR11, COOH, COOR11, NH_2, NHCOR11, NHR11, NR11R12, halogen, or phenyl, wherein the residues R11 und R12 independently can have the above indicated meanings.

Preferred heteroaryls are:



The term "ring system" generally refers to rings with 3, 4, 5, 6, 7, 8, 9, or 10 members. Preferred are rings with 5 and 6 members. Furthermore, ring systems with one or 2 annelated rings are preferred.

The compounds of Formula I may be present as such, or, if they contain acidic or basic groups, in the form of their salts with physiologically tolerable bases or acids. Examples for such acids are: hydrochloric acid, citric acid, trifluoracetic acid, tartaric acid, lactic acid, phosphoric acid, methane sulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid, succinic acid, hydroxysuccinic acid, sulfuric acid, glutaric acid, aspartic acid, pyruvic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid, and acetylglycine. Examples for

bases are alkali ions, preferably Na, K, particularly preferred the tri-potassium and tri-sodium salts, alkaline earth ions, preferably C, Mg, ammonium ions.

The compounds according to the invention may be administered orally in the usual way. The application may also be i.v., i.m., with vapors, or sprays through the nasopharynx.

The dosage depends on age, condition and weight of the patient as well as on the type of application. Usually, the daily dose of the active ingredient per person is between 0.1 µg/kg and 1 g/kg orally. This dosage may be given as 2 to 4 split dosages, or once per day as a slow release form.

The novel compounds may be used in the usual solid or liquid pharmaceutical application forms, e.g. as tablets, film tablets, capsules, powder, granules, coated tablets, solutions, or sprays. These are produced in the usual way. The agents can be processed with the usual pharmaceutical adjuvants such as tablet binders, fillers, preservatives, disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, retardation agents, antioxidants, and/or propellants (see H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). Usually, the so obtained application forms contain the active ingredient in amounts of 0.1 to 99 percent per weight.

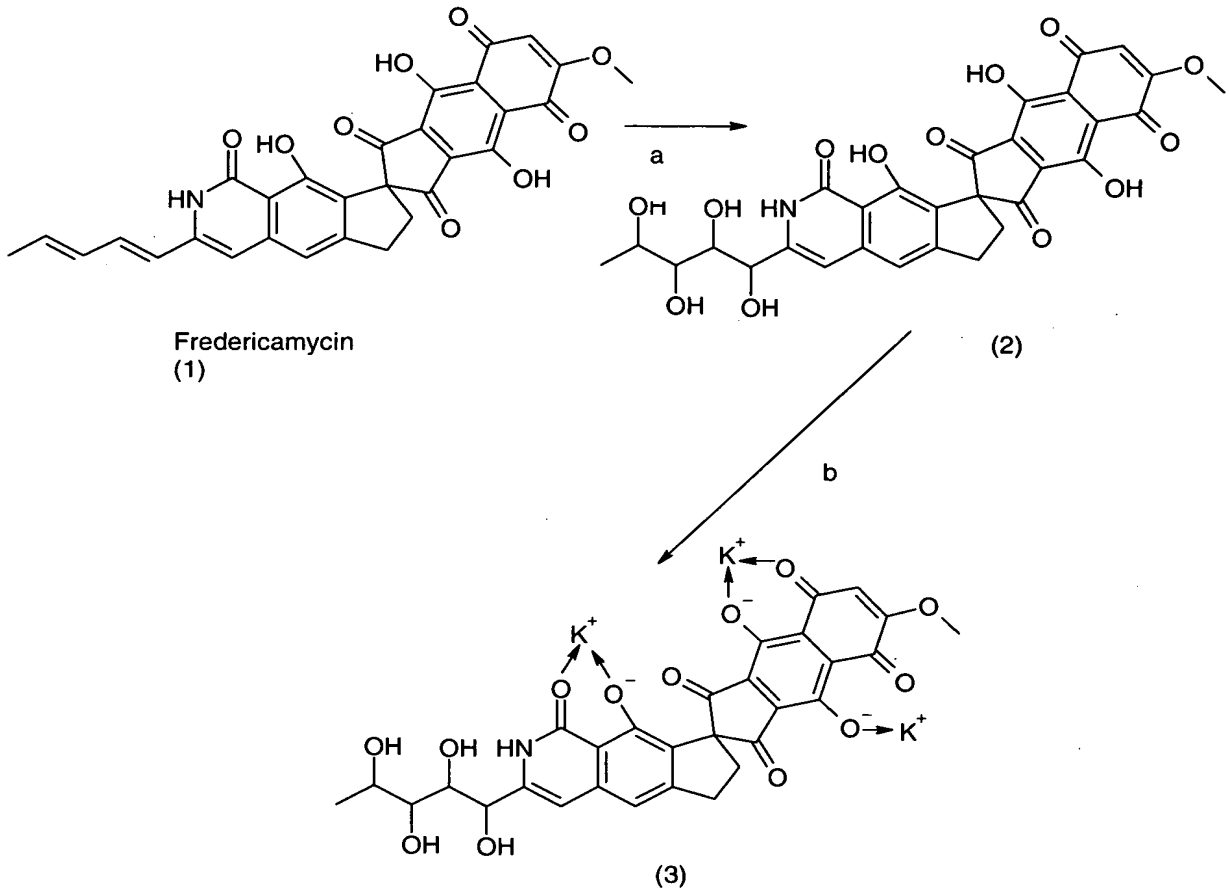
Experimental Part

Fredericamycin A can be prepared by fermentation or fully synthetically according to the known methods. The reduced forms of the Formulas Ib and IIb can be obtained from the appropriate compounds of Formulas Ia and IIa using mild reducing agents.

Preparation of the substances

For synthesis of water soluble fredericamycin derivatives, fredericamycin (1) was first hydroxylized with osmium(IV)oxide at the diene side chain. The resulting compound (2) shows significantly higher water solubility compared to the original compound fredericamycin (1). In order to further increase the water solubility, (2) was transformed into the tri-potassium salt (3) (see diagram 1).

Diagram 1

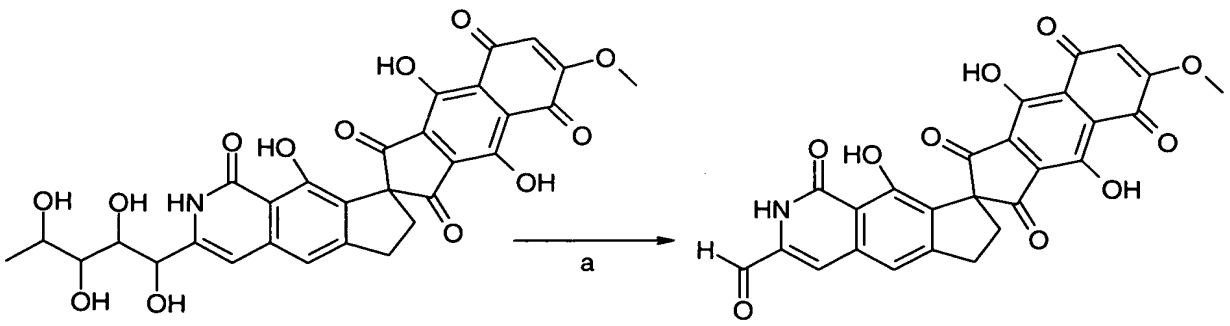


a) OsO_4, N-methylmorpholine-N-oxide, CH_2, Cl_2, CH_3OH, H_2O

b) KOH pyridine

The fredericamycin tetrol (2) serves, among others, as an important intermediate for the synthesis of other fredericamycin derivatives with increased solubility and/or better action profile. By iodate cleavage with sodium periodate or carrier-bound periodate, the tetrol side chain may be degraded with very high yields to fredericamycin aldehyde (4) (see diagram 2).

Diagram 2



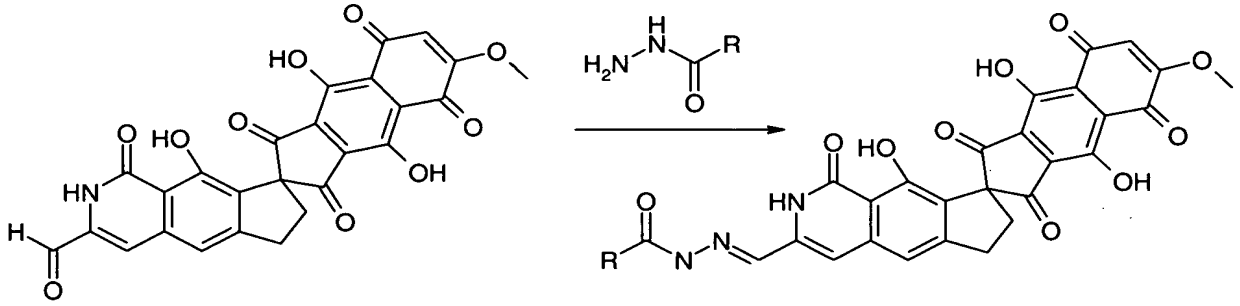
(2) (4)

a) $NaIO_4$-H_2O-DMF or carrier bound -IO_4-H_2O-DMF

The fredericamycin aldehyde (4) can be reacted with acylhydrazones, hydroxylamine, and O-alkylhydroxylamine to the appropriate hydrazone (see diagram 3), or oxime and oximether (see diagram 4). The reaction can be performed at room temperature in solvents such as DMF or pyridine, and is finished after a few minutes to hours.

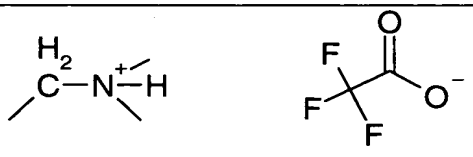
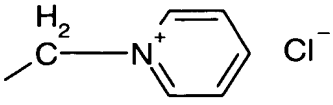
Synthesis of hydrazones

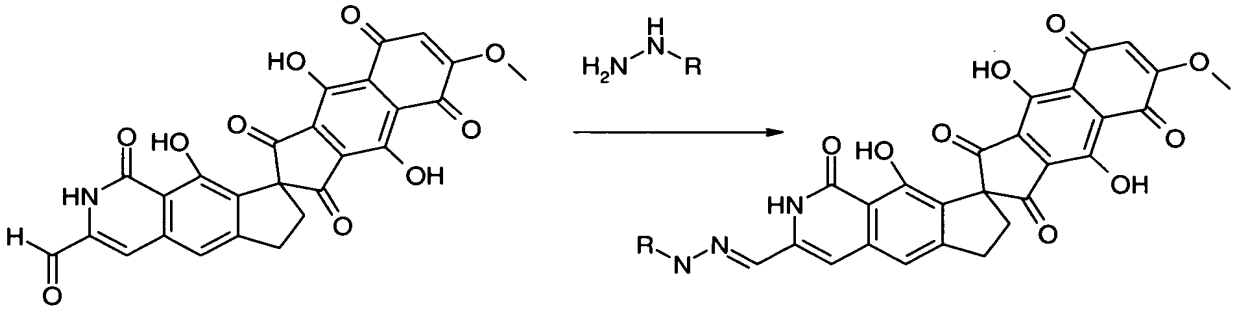
Diagram 3



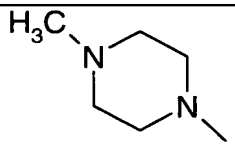
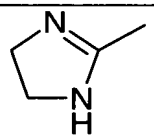
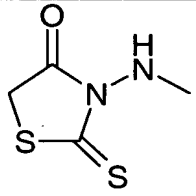
(4) (Table 1/3)

Table 1

Example/compound	R	m/e	λ_{max}(nm)
5/118		601.3	504.0
6/119		635.2	486.0

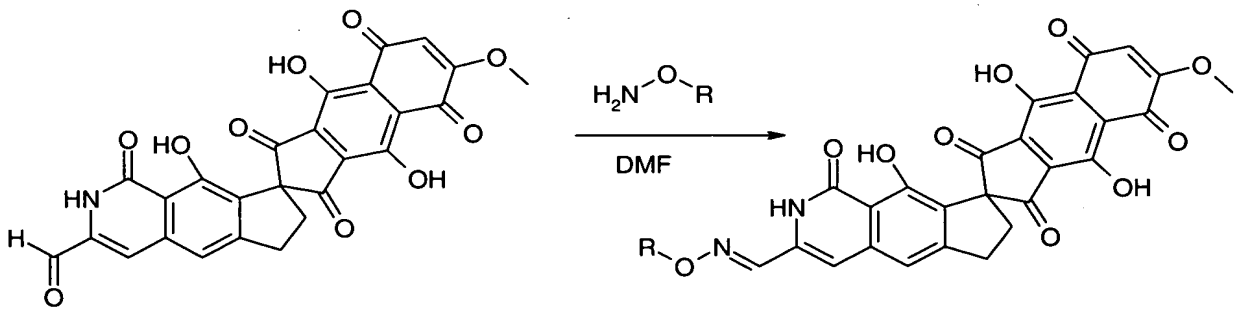


(4)

R	Compound	Example
	111	18
	105	19
	113	20

Synthesis of oximether

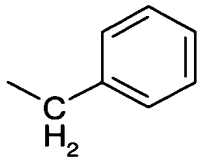
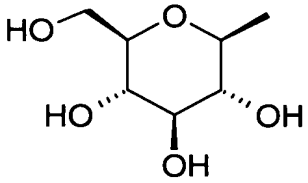
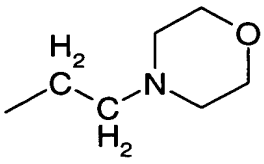
Diagram 4



(4)

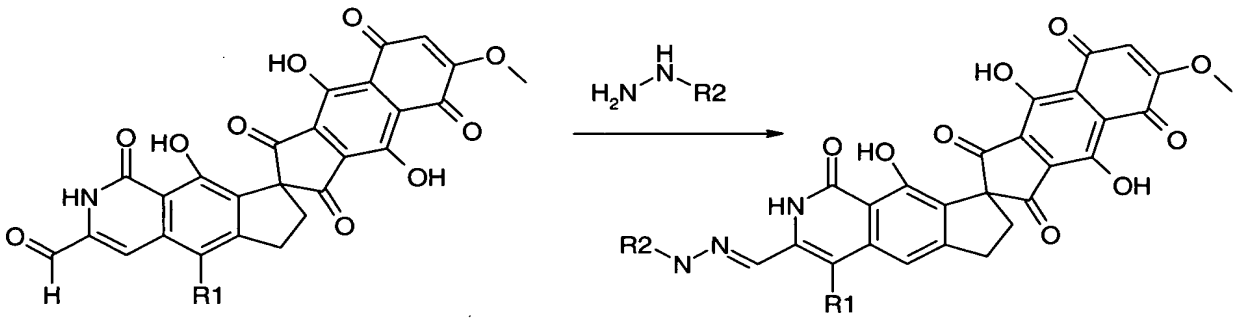
(Table 2/3)

Table 2

Example/compound	R	m/e	λ_{max}(nm)
7/122	-H	516.1	500.0
8/120	$-CH_3$	531.2	500.0
9/121		607.2	504.0
10/123		678.1	504.0
21/116		630.1	504.0

Analogously, the compounds 100 – 242 can be generated according to the instructions below (table 3). The hereby used hydrazines, hydrazones and hydroxylamines are available commercially, or have been produced according to instructions known from the literature.

Diagram 5

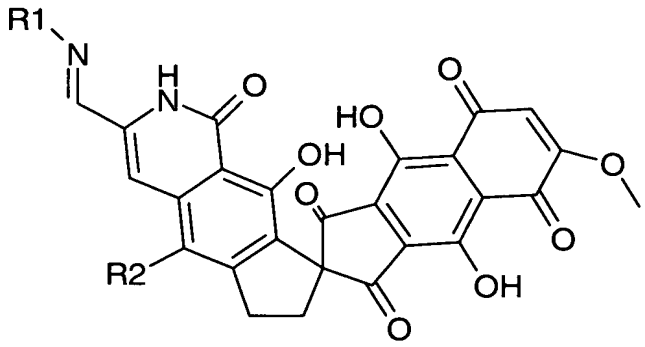


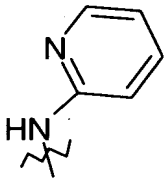
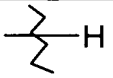
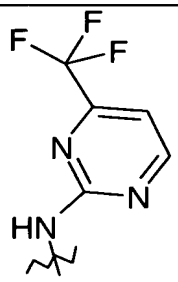
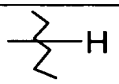
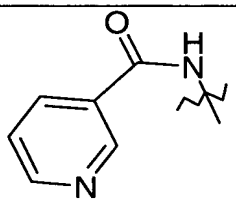
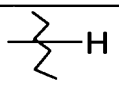
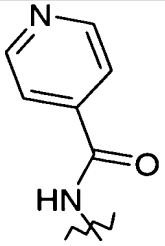
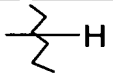
(R1 = Halogen, I, Br, Cl)

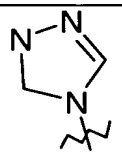
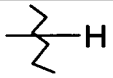
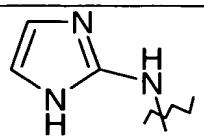
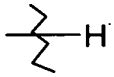
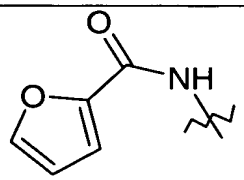
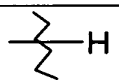
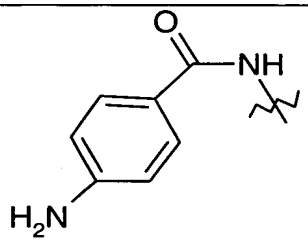
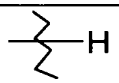
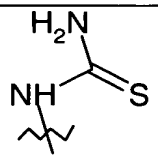
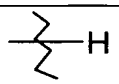
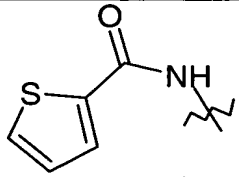
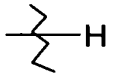
(Table 3)

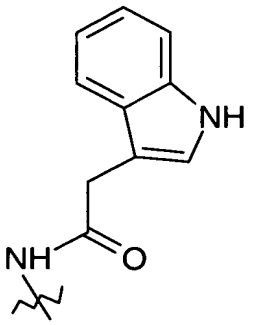
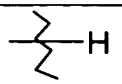
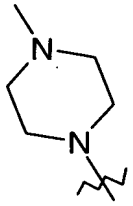
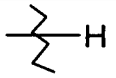
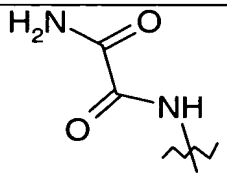
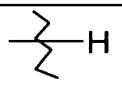
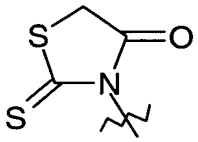
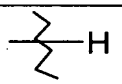
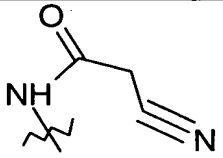
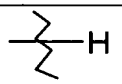
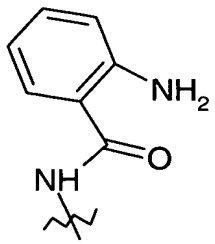
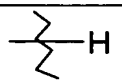
Table 3

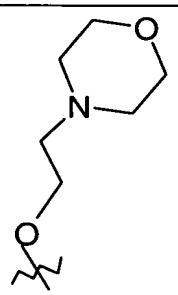
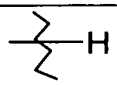
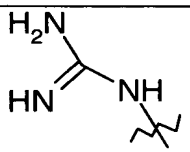
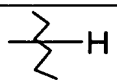
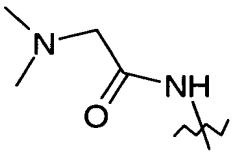
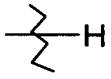
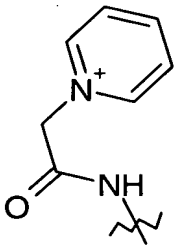
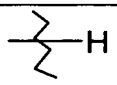
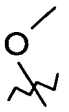
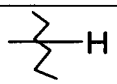
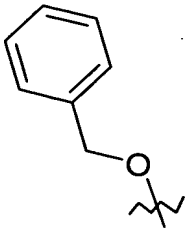
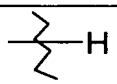
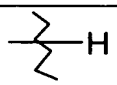
Formula for table 3:

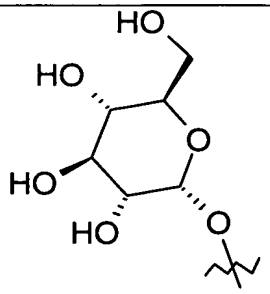
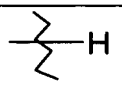
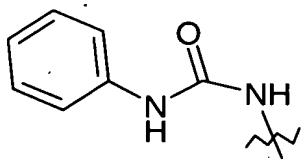
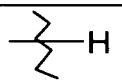
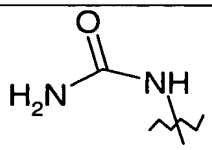
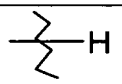
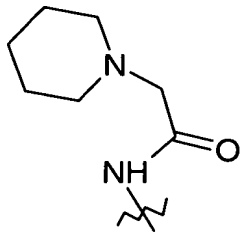
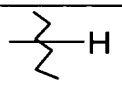
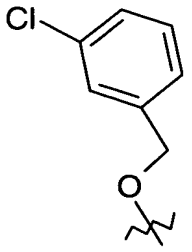
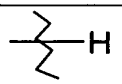


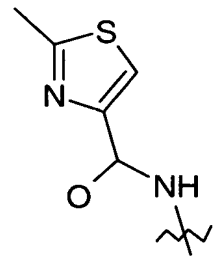
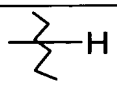
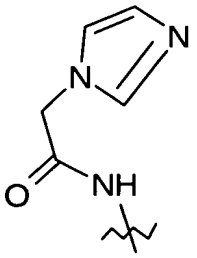
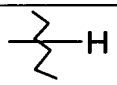
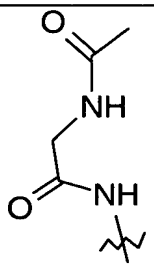
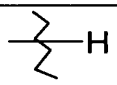
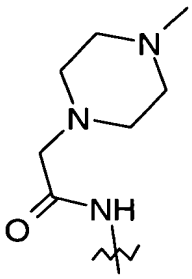
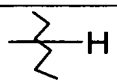
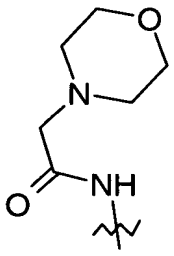
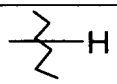
Example/Compound	R1	R2	Calculated mass	Actual mass	UV_{max}	Yield
100	 $C_5H_5N_2$	 H	592.1230	593.10	500	95
101	 $C_5H_3F_3N_3$	 H	661,1056	662,11	500	95
102	 $C_6H_5N_2O$	 H	620,1179	621,11	492	95
103	 $C_6H_5N_2O$	 H	620,1179	621,11	500	95

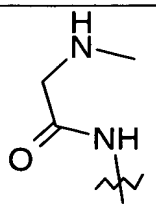
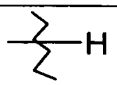
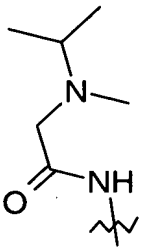
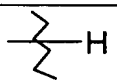
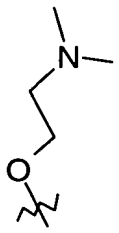
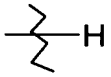
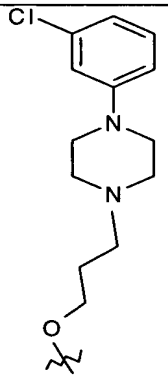
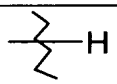
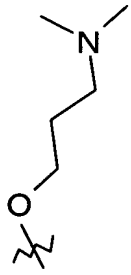
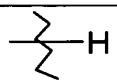
104	 $C_2H_2N_3$	 H	567,1026	568,11	500	80
105 (19)	 $C_3H_6N_3$	 H	583,1339	584,10	492	95
106	 $C_5H_4NO_2$	 H	609,1019	610,09	492	95
107	 $C_7H_7N_2O$	 H	634,1335	635,13	492	95
108	 $NHCSNH_2$	 H	574,0794	558,05	492	95
109	 C_5H_4NOS	 H	625,0791	626,08	492	95

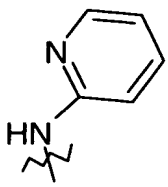
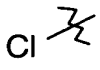
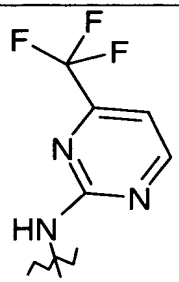
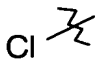
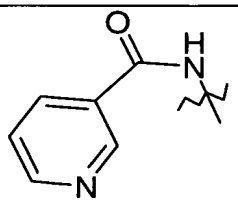
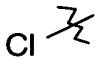
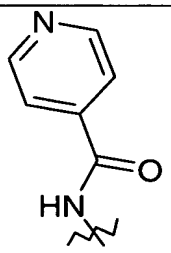
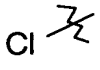
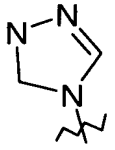
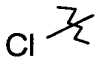
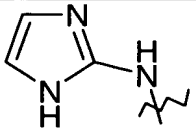
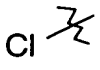
110	 $C_{10}H_9N_2O$	 H	672,1492	673,15	492	95
111	 $C_5H_{11}N_2$	 H	598,1699	599,14	492	95
112	 $C_2H_3N_2O_2$	 H	586,0971	587,10	492	95
113 (20)	 $C_3H_2NOS_2$	 H	631,0,55	632,05	500	95
114	 $C_3H_3N_2O$	 H	582,1022	583,13	492	95
115	 $C_7H_7N_2O$	 H	634,1335	635,16	492	70

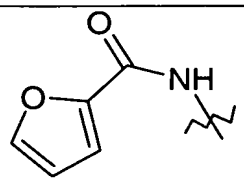
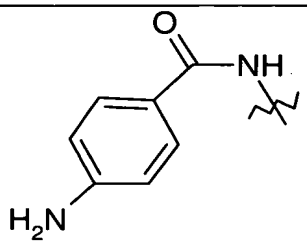
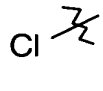
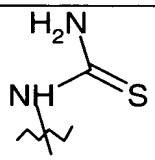
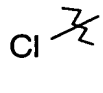
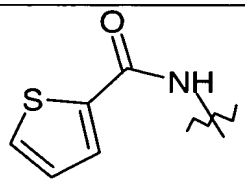
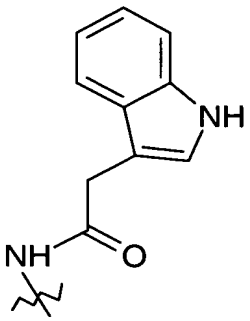
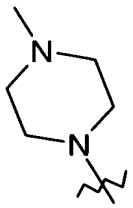
116	 $C_6H_{12}NO_2$	 H	629,1645	630,14	492	85
117	 CH_4N_3	 H	557,1182	558,11	500	95
118	 $C_4H_9N_2O$	 H	600,1492	601,16	492	85
119	 $C_7H_8N_2O$	 H	635,1414	635,13	495	85
120 (8)	 OMe	 H	530,0961	531,12	492	90
121 (9)	 OCH_2Ph	 H	606,1274	607,16	492	95
122			516,0804	517,11	482	95

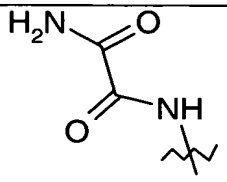
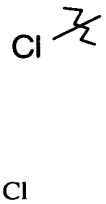
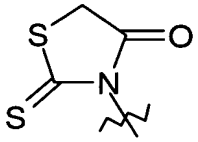
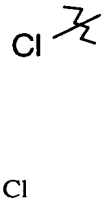
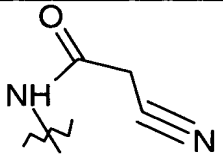
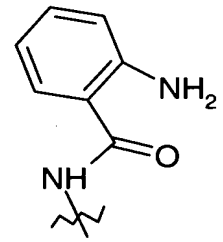
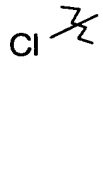
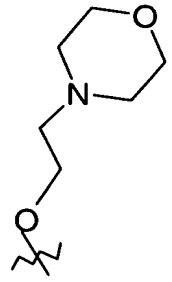
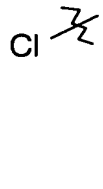
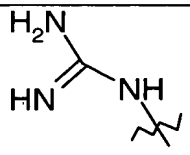
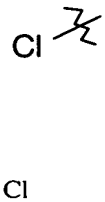
	OH	H				
123 (10)	 $C_6H_{11}O_6$	 H	678,1332	679,14	500	95
124	 $C_7H_7N_2O$	 H	634,1335	635,15	492	95
125	 $NHCONH_2$	 H	558,1022	559,12	492	95
126	 $C_7H_{13}N_2O$	 H	640,1805	614,13	492	95
127	 C_7H_6ClO	 H	640,0884	641,10	492	95

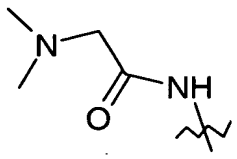
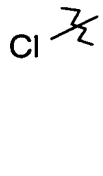
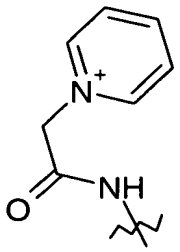
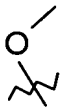
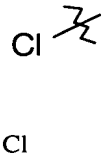
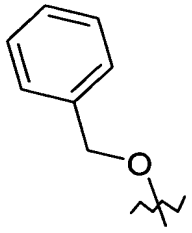
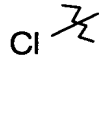
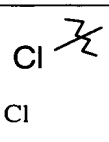
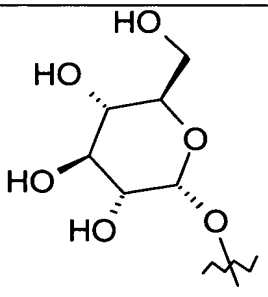
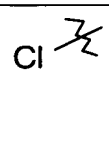
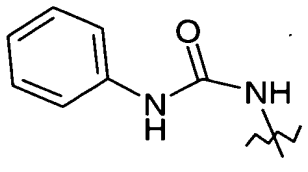
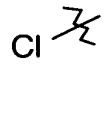
128	 $C_5H_5N_2OS$	 H	640,0900	641,10	492	95
129	 $C_5H_6N_3O$	 H	623,1288	624,13	500	90
130	 $C_4H_7N_2O_2$	 H	614,1284	615,13	492	95
131	 $C_7H_{14}N_3O$	 H	655,1914	656,19	492	50
132	 $C_6H_{11}N_2O_2$	 H	642,1597	643,17	492	60

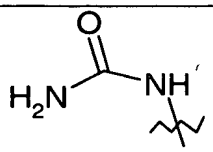
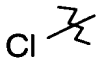
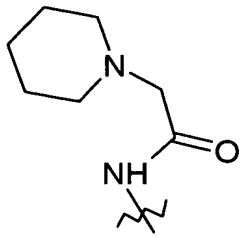
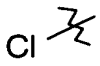
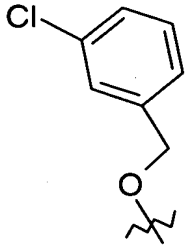
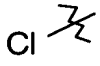
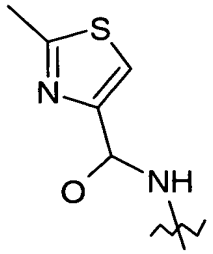
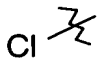
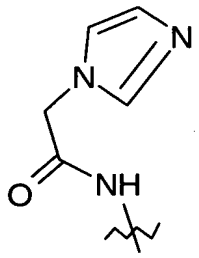
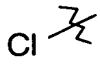
133	 $C_3H_7N_2O$	 H	586,1335	587,15	492	70
134	 $C_6H_{13}N_2O$	 H	628,1805	629,17	492	70
135	 $C_4H_{10}NO$	 H	587,1539	588,14	492	90
136	 $C_{13}H_{18}ClN_2O$	 H	752,1885	753,19	492	85
137	 $C_5H_{12}NO$	 H	601,1696	602,19	492	70

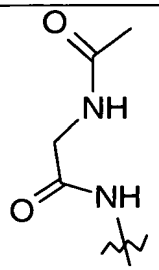
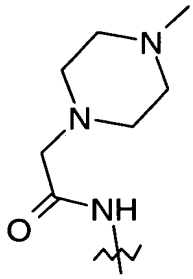
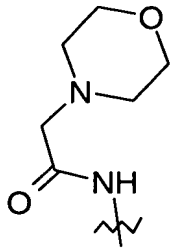
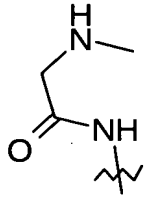
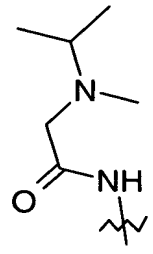
138	 $C_5H_5N_2$	 Cl	626,0840	627,07	500	95
139	 $C_5H_3F_3N_3$	 Cl	695,0666	696,06	500	95
140	 $C_6H_5N_2O$	 Cl	654,0789	655,07	500	95
141	 $C_6H_5N_2O$	 Cl	654,0789	655,07	500	95
142	 $C_2H_2N_3$	 Cl	601,0636	602,06	500	90
143	 $C_3H_6N_3$	 Cl	617,0949	618,08	500	95

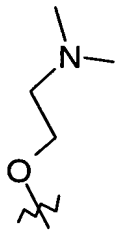
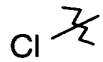
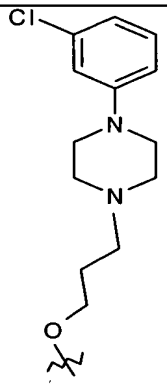
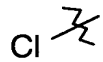
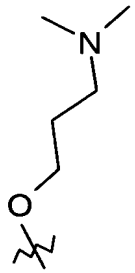
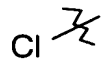
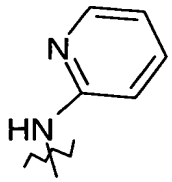
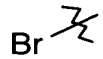
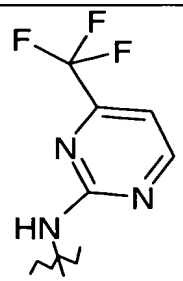
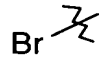
144	 $C_5H_4NO_2$		643,0629	644,05	500	95
145	 $C_7H_7N_2O$		668,0946	669,07	500	95
146	 $NHCSNH_2$		608,0404	609,07	500	95
147	 C_5H_4NOS		659,0401	660,07	500	95
148	 $C_{10}H_9N_2O$		706,1102	707,16	500	95
149	 $C_5H_{11}N_2$		632,1309	633,16	500	95

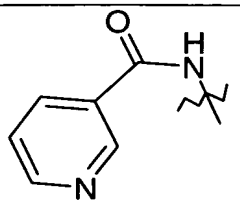
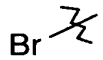
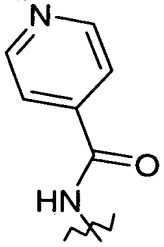
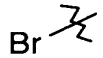
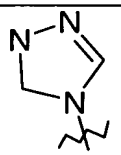
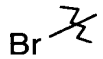
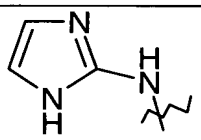
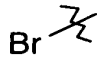
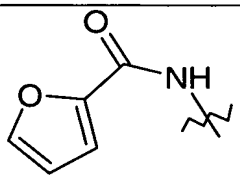
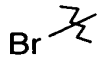
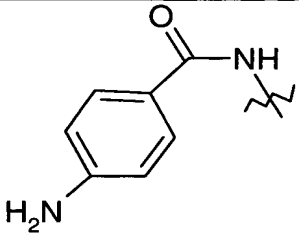
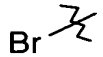
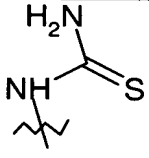
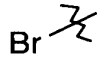
150	 $C_2H_3N_2O_2$		620,0582	621,09	500	95
151	 $C_3H_2NOS_2$		664,9965	645,31	500	95
152	 $C_3H_3N_2O$		616,0633	617,10	500	95
153	 $C_7H_7N_2O$		668,0946	669,13	500	95
154	 $C_6H_{12}NO_2$		663,1255	664,16	500	95
155	 CH_4N_3		591,0792	592,11	500	95

156	 $C_4H_9N_2O$		634,1102	635,14	500	95
157	 $C_7H_8N_2O$		669,1024	669,12	500	95
158	 OMe		564,0571	565,09	500	95
159	 OCH_2Ph		640,0884	641,12	500	95
160	 OH		550,0415	551,06	500	95
161	 $C_6H_{11}O_6$		712,0943	713,10	500	95
162			668,0946	669,09	500	95

	$C_7H_7N_2O$	Cl				
163	 $NHCONH_2$	 Cl	592,0633	593,07	500	90
164	 $C_7H_{13}N_2O$	 Cl	674,1415	675,11	500	95
165	 C_7H_6ClO	 Cl	674,0494	675,03	500	90
166	 $C_5H_5N_2OS$	 Cl	674,0510	675,02	500	95
167	 $C_5H_6N_3O$	 Cl	657,0898	658,06	500	95

168	 $C_4H_7N_2O_2$		648,0895	649,07	500	95
169	 $C_7H_{14}N_3O$		689,1524	690,15	500	60
170	 $C_6H_{11}N_2O_2$		676,1208	677,13	500	60
171	 $C_3H_7N_2O$		620,0946	621,11	500	70
172	 $C_6H_{13}N_2O$		662,1415	663,12	500	70

173	 $C_4H_{10}NO$	 Cl	621,1150	622,10	500	60
174	 $C_{13}H_{18}ClN_2O$	 Cl	786,1495	787,16	500	90
175	 $C_5H_{12}NO$	 Cl	635,1306	636,10	500	75
176	 $C_5H_5N_2$	 Br	670,0334	670,99	500	95
177	 $C_5H_3F_3N_3$	 Br	739,0161	739,99	500	95

178	 $C_6H_5N_2O$	 Br	698,0284	699,00	500	90
179	 $C_6H_5N_2O$	 Br	698,0284	699,00	500	90
180	 $C_2H_2N_3$	 Br	645,0130	645,99	492	70
181	 $C_3H_6N_3$	 Br	661,0443	662,01	492	95
182	 $C_5H_4NO_2$	 Br	687,0124	688,99	492	95
183	 $C_7H_7N_2O$	 Br	712,0440	713,03	500	95
184		 Br	651,9899	653,04	500	95

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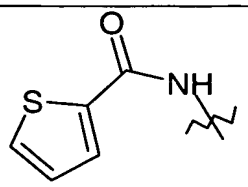
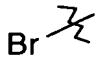
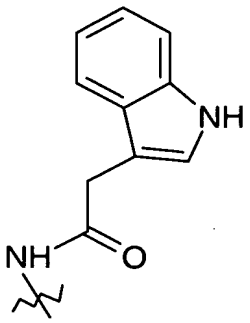
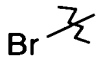
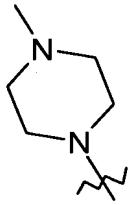
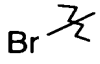
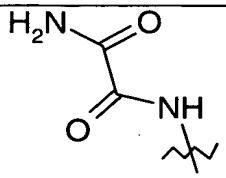
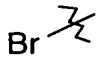
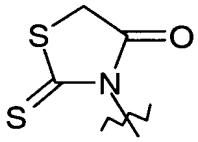
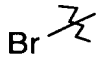
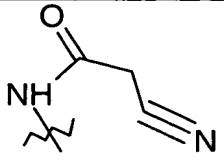
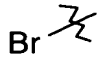
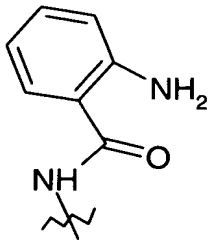
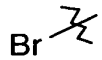
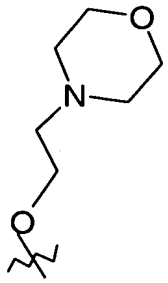
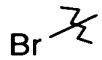
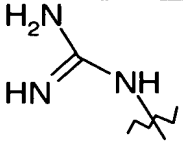
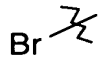
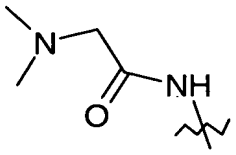
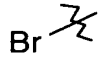
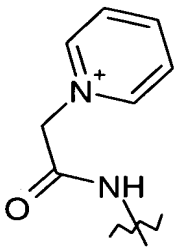
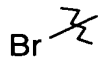
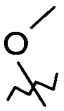
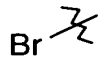
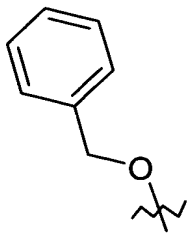
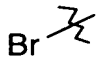
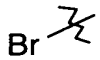
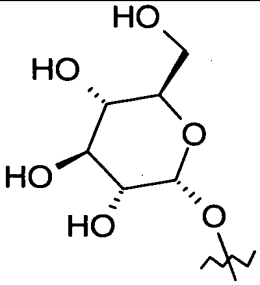
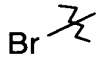
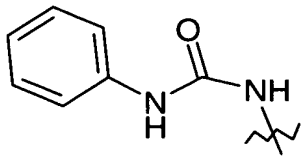
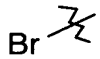
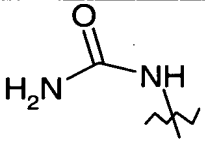
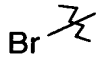
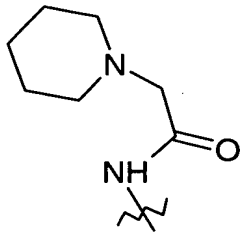
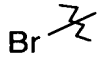
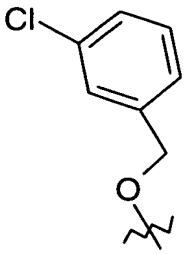
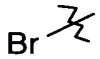
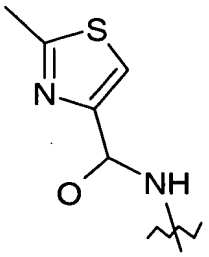
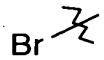
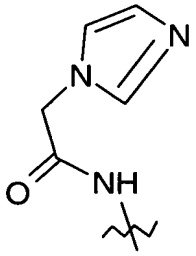
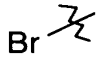
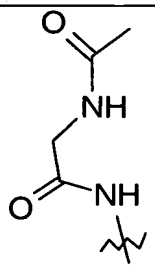
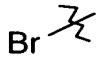
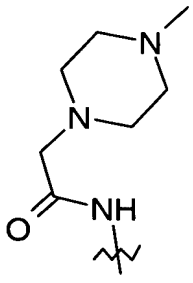
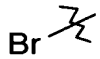
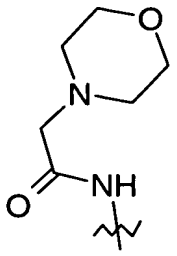
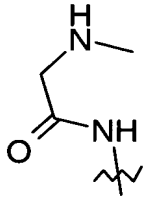
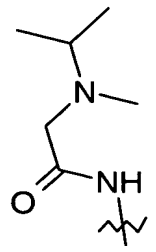
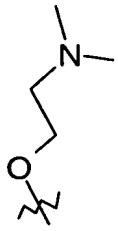
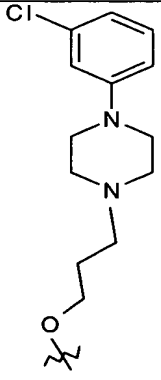
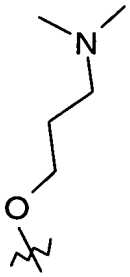
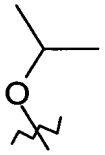
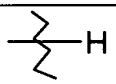
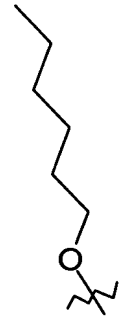
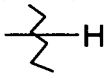
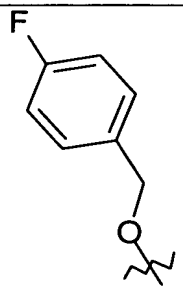
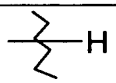
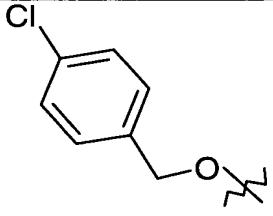
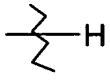
185	 C_5H_4NOS	 Br	702,9895	704,02	492	95
186	 $C_{10}H_9N_2O$	 Br	750,0597	751,10	500	95
187	 $C_5H_{11}N_2$	 Br	676,0804	677,10	492	95
188	 $C_2H_3N_2O_2$	 Br	664,0076	665,05	500	95
189	 $C_3H_2NOS_2$	 Br	708,9460	709,99	492	95
190	 $C_3H_3N_2O$	 Br	660,0127	661,05	492	95

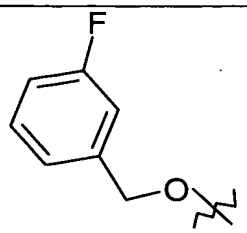
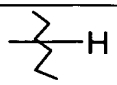
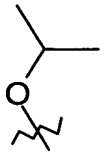
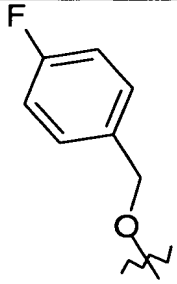
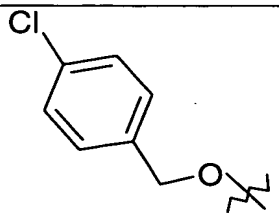
191	 $C_7H_7N_2O$	 Br	712,0440	713,08	492	70
192	 $C_6H_{12}NO_2$	 Br	707,0750	708,06	500	95
193	 CH_4N_3	 Br	635,0287	636,02	500	95
194	 $C_4H_9N_2O$	 Br	678,0597	679,06	500	95
195	 $C_7H_8N_2O$	 Br	713,0518	713,03	500	95
196	 OMe	 Br	608,0066	609,03	492	95

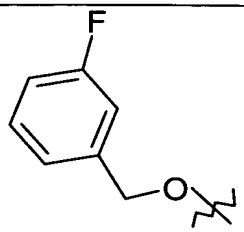
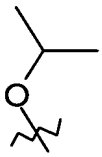
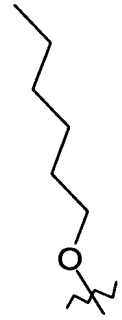
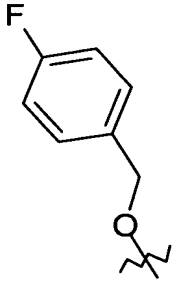
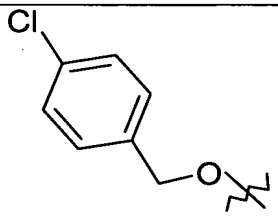
197	 OCH_2Ph	 Br	684,0379	685,05	492	95
198	 OH	 Br	593,9909	595,01	492	95
199	 $C_6H_{11}O_6$	 Br	756,0437	757,00	500	90
200	 $C_7H_7N_2O$	 Br	712,0440	713,00	500	90
201	 $NHCONH_2$	 Br	636,0127	637,00	492	90
202	 $C_7H_{13}N_2O$	 Br	718,0910	719,00	500	90

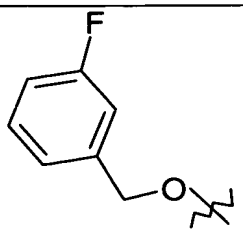
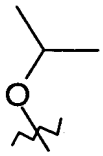
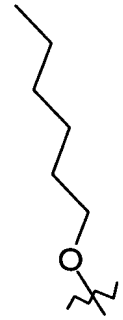
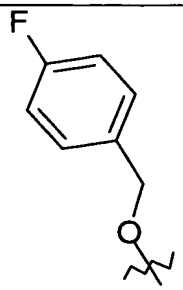
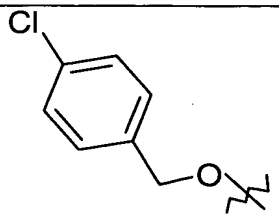
203	 C_7H_6ClO	 Br	717,9989	718,00	492	95
204	 $C_5H_5N_2OS$	 Br	718,0004	718,97	492	95
205	 $C_5H_6N_3O$	 Br	701,0392	702,01	500	95
206	 $C_4H_7N_2O_2$	 Br	692,0389	693,03	492	95
207	 $C_7H_{14}N_3O$	 Br	733,1018	734,10	500	90

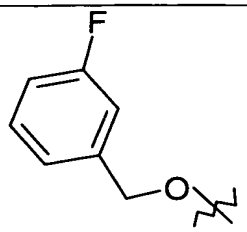
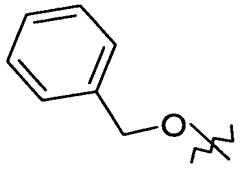
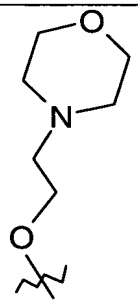
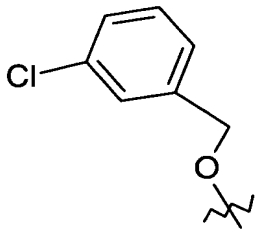
208	 $C_6H_{11}N_2O_2$		720,0702	721,10	500	95
209	 $C_3H_7N_2O$		664,0440	665,08	500	95
210	 $C_6H_{13}N_2O$		706,0910	707,09	500	90
211	 $C_4H_{10}NO$		665,0644	666,08	500	95
212	 $C_{13}H_{18}ClN_2O$		830,0989	831,11	500	95

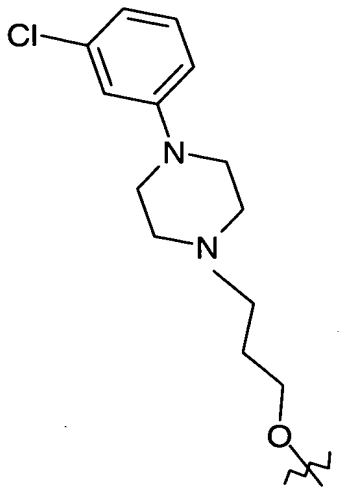
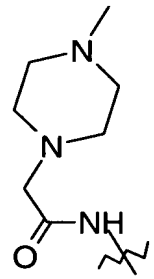
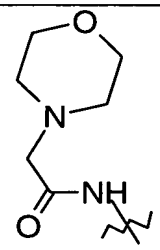
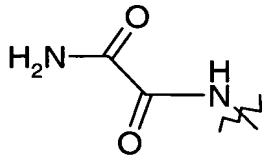
213	 $C_5H_{12}NO$	 Br	679,0801	680,09	492	95
214	 Oi-Pr	 H	558,1274	559,21	500	99
215	 O-n-hex	 H	600,1743	601,30	500	99
216	 C_7H_6FO	 H	624,1180	625,28	500	99
217	 C_7H_6ClO	 H	640,0884	641,27	500	99

218	 C_7H_6FO	 H	624,1180	625,31	500	99
219	 Oi-Pr	 Cl	592,0884	593,28	500	80
220	 O-n-hex	 Cl	634,1354	635,36	500	90
221	 C_7H_6FO	 Cl	658,0790	659,32	500	85
222	 C_7H_6ClO	 Cl	674,0494	675,31	500	80

223	 C_7H_6FO	 Cl	658,0790	659,34	500	80
224	 Oi-Pr	 Br	636,0379	639,30	492	90
225	 O-n-hex	 Br	678,0848	679,37	492	95
226	 C_7H_6FO	 Br	702,0284	703,34	492	95
227	 C_7H_6ClO	 Br	717,9989	719,34	492	95

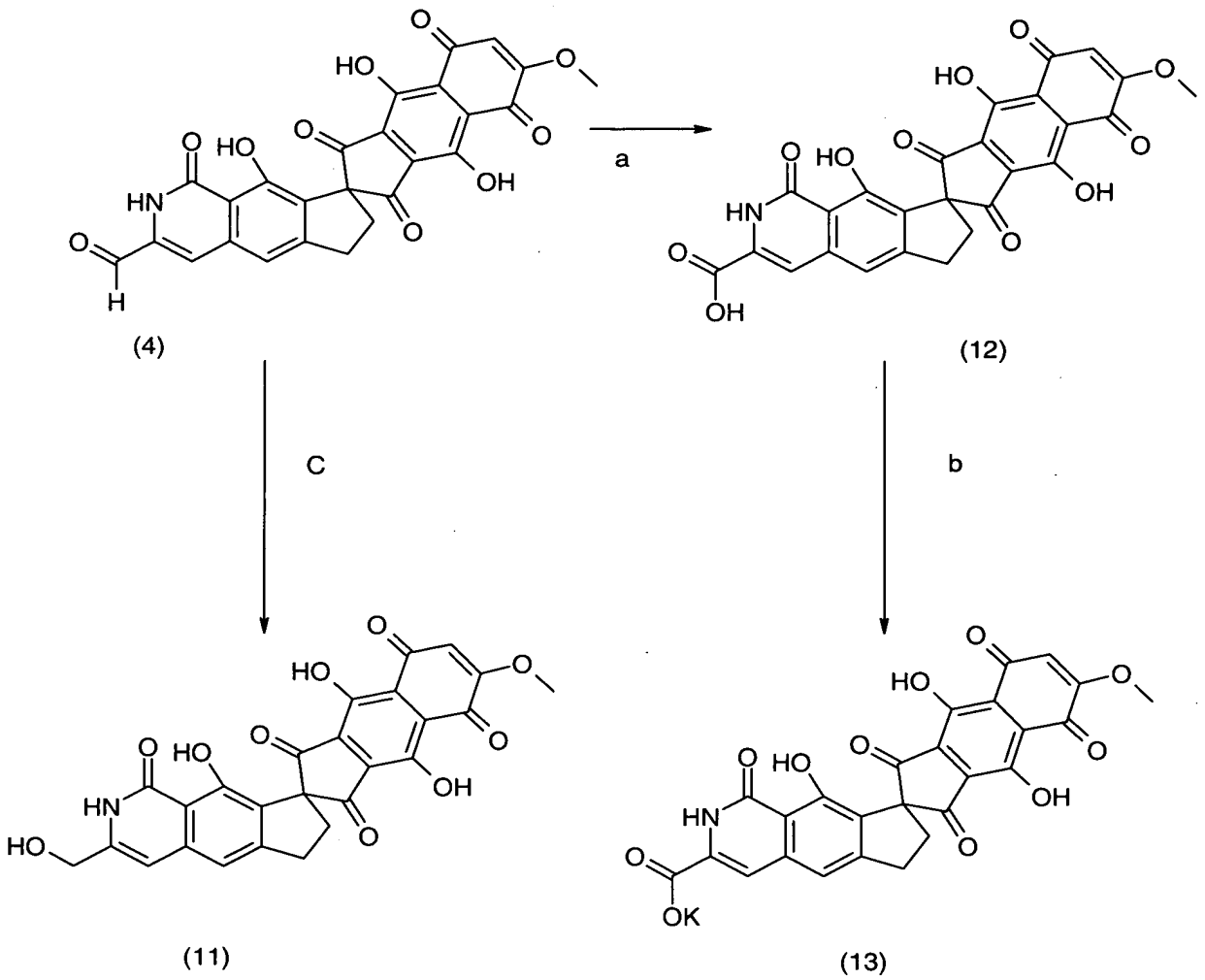
228	 C_7H_6FO	 Br	702,0284	705,35	492	95
229	 Oi-Pr	 I	684,0200	685,30	500	99
230	 O-n-hex	 I	726,0669	727,41	500	99
231	 C_7H_6FO	 I	750,0105	751,38	500	99
232	 C_7H_6ClO	 I	765,9810	767,36	500	99

233	 C_7H_6FO		750,0105	751,38	500	99
234	 OCH_2Ph		732,0200	733,38	500	99
235	 $C_6H_{12}NO_2$		755,0571	756,33	500	99
236	 OMe		655,9887	657,32	492	95
237	 C_7H_6ClO		765,9810	767,38	492	99

238	 $C_{13}H_{18}ClN_2O$	 I	878,0810	879,45	500	99
239	 OH	 I	641,9730	643,31	492	99
240	 $C_7H_{14}N_3O$	 I	781,0840	782,39	500	99
241	 $C_6H_{11}N_2O_2$	 I	768,0523	769,38	500	99
242	 $C_2H_3N_2O_2$	 I	711.9897	713.37	500	99

Reduction and oxidation of fredericamycin aldehyde (4)

Fredericamycin aldehyde (4) can be reacted with a common reducing agent such as sodium borohydrid in a solvent such as DMF or pyridine to hydroxymethyl fredericamycin (11). The reaction can be summarized as a single pot reaction (iodate cleavage of fredericamycin tetrol (2) to fredericamycin aldehyde (4) (see diagram 2) and reduction without isolation of the intermediates to fredericamycin alcohol (11)).



a) $NaClO_2$, NaH_2PO_4, 2,3-dimethylbutene-2

b) KOH, $-H_2O$, DMF

c) $NaBH_4$

Fredericamycin aldehyde (4) can be oxidized with the oxidizing agent sodium chlorite ($NaClO_2$), a buffer such as sodium dihydrogenphosphate in presence of an alkene such as 2,3-dimethylbutene with very good yields to fredericamycin carboxylic acid (12). The usually employed oxidation methods such as those being used in preparative chemistry for the oxidation of aldehydes to carboxylic acids (oxidation with chromium(VI) compounds,

manganese(VII) compounds as well as peroxo acid) did not lead to success. Only the use of the above described oxidation method provided the desired product. The literature describes oxidations of 2-pyridone-6-aldehydes with silver ions and potassium permanganate in an alkaline medium. This method, however, is not suited for fredericamycin and its derivatives since fredericamycin (1) contains base-labile (-reactive) groups (OH groups) causing undesired side reactions.

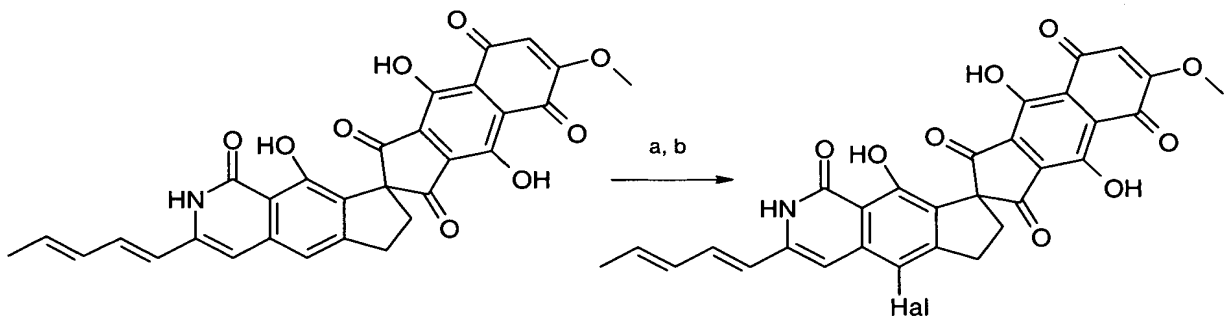
The potassium salt of the fredericamycin acid (13) was obtained according to a common method by stoichiometric neutralization.

Substitution in the B ring

Fredericamycin (1) can be reacted with halogenation agents such as N-bromosuccinimide (NBS) and N-iodosuccinimide (NIS) with good yields to the substituted 5-bromo or 5-iodo fredericamycin derivatives (14) and (15) (diagram 6). The fredericamycin aldehyde (4) and (36) can be transformed with elemental bromine, NBS, BrI, NIS, and NCS to the appropriate halogen-substituted fredericamycin aldehyde (37), (38) and (39).

The appropriate fluorine compound is accessible, too.

Diagram 6

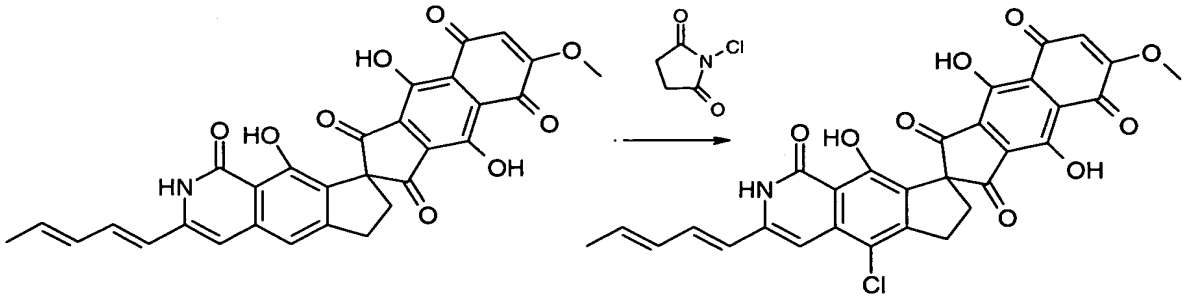


Fredericamycin

Hal: Br (14), I (15)

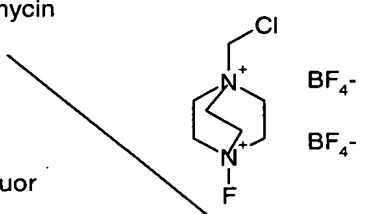
a) N-bromosuccinimide, DMF, 0° C;

b) N-iodosuccinimide, DMF, 0° C;

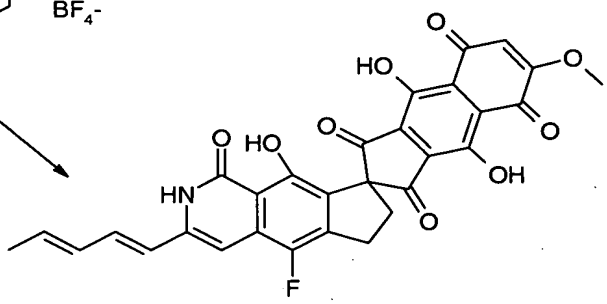


Fredericamycin

34



Selectfluor



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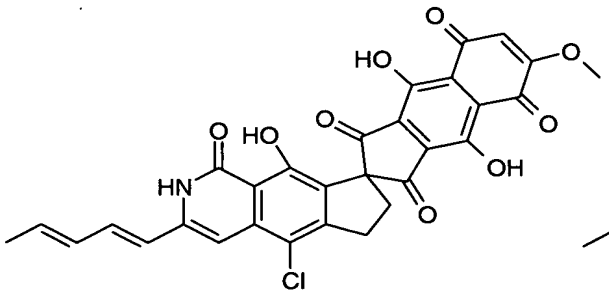

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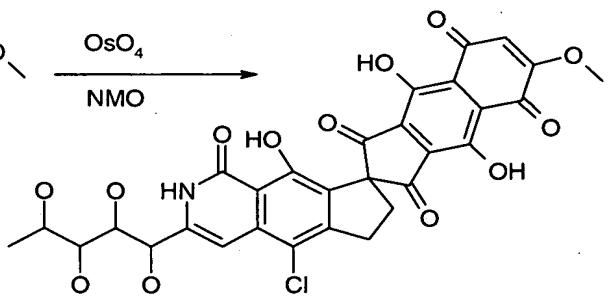

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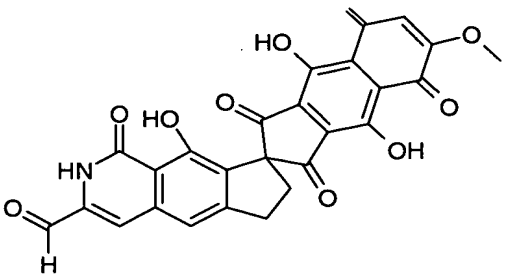
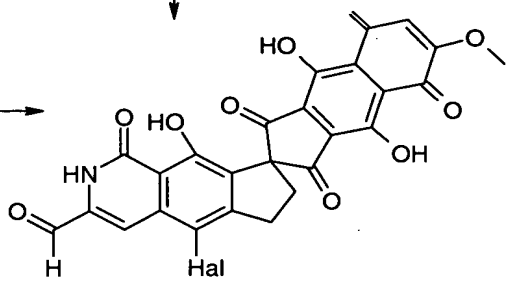


(4)

Fredericamycinaldehyde

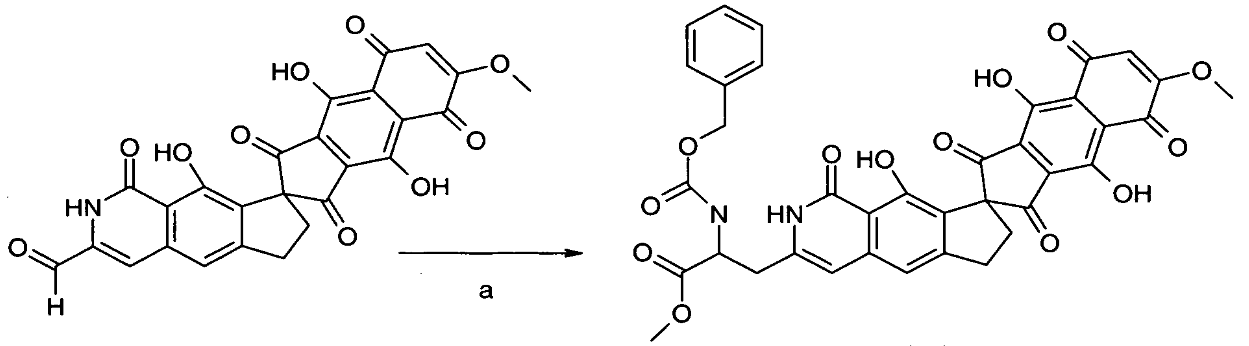


Br: (37)
I: (38)
Cl: (39)

Both of the two following fredericamycin compounds (23) and (24) are also precursors. (23) is the precursor for an amino acid-linked fredericamycin derivative.

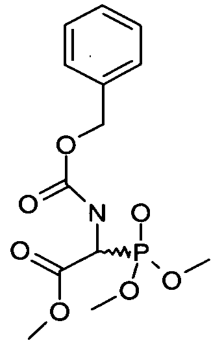
The preparation of (23) may be recognized as proof that the aldehyde (4) may be reacted with phosphorylides according to Wittig or Wittig-Horner (see diagram 7).

Diagram 7



(4) (23)

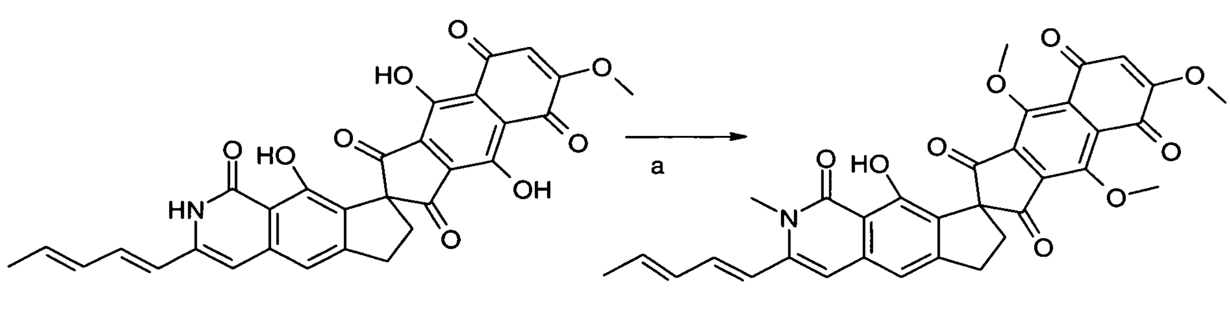
(a)



, Tetramethyl guanidine

The compound (24) is the precursor of an N-methylated fredericamycin derivative (diagram 8).

Diagram 8

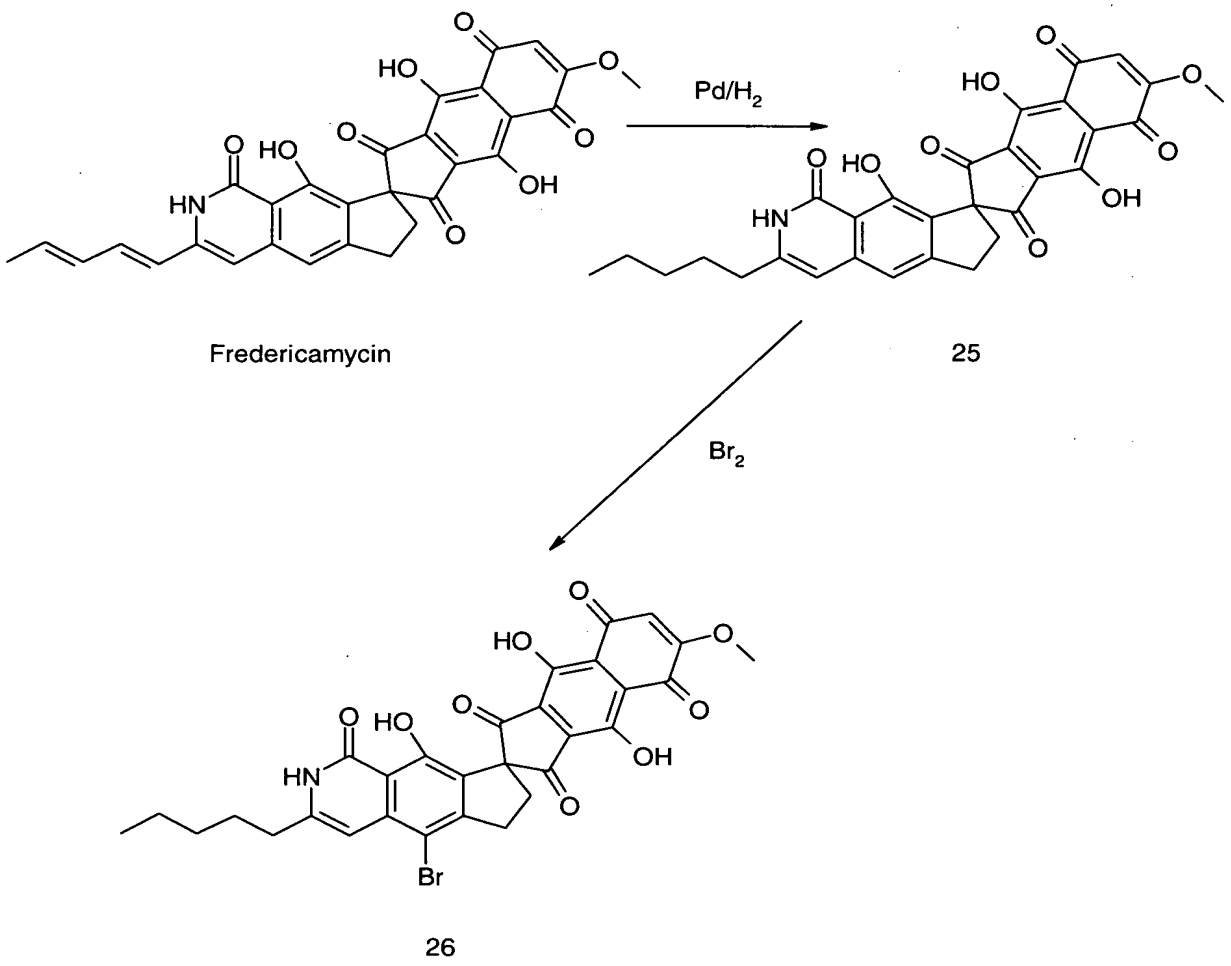


(1) (24)

a) CH_3I, K_2CO_3, DMF, RT

Fredericamycin may be transformed by palladium/hydrogen almost quantatively to tetrahydro fredericamycin (25), and may be halogenated in the nucleus according to the above described methods, e.g. to the bromine compound (26) (diagram 9):

Diagram 9



Fredericamycin

25

26

Surprisingly it has also been found that the methoxy groups in fredericamycin and the derivatives according to the invention can be exchanged under alkali or earth alkali acetate catalysis by oxygen nucleophiles such as alcohols or polyols. Thereby, the alcohols can carry a multitude of different substituents (table 4).

Diagram 10

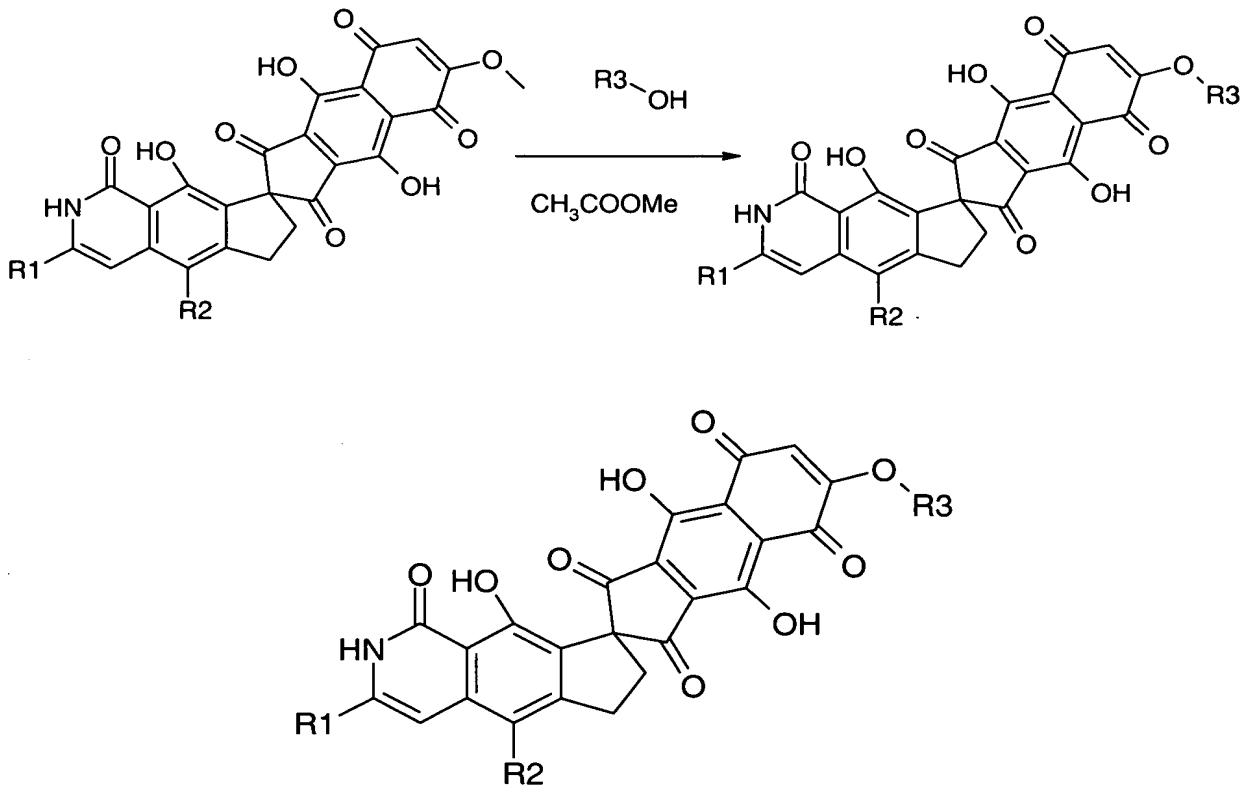
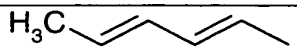
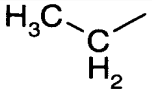
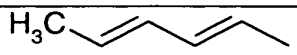
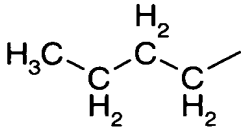
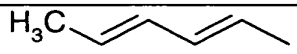
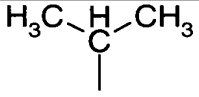
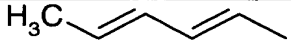
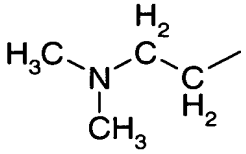
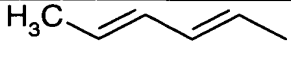
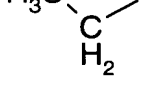
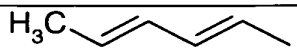
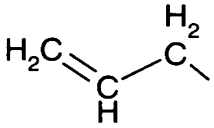
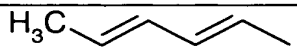
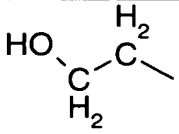
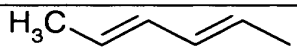
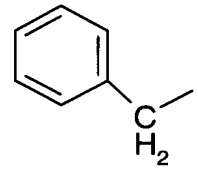
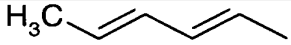
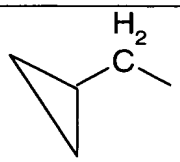
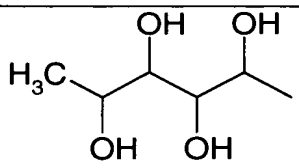
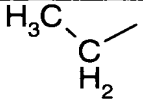
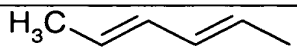
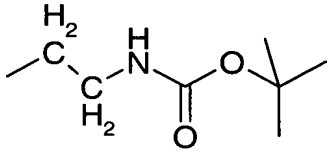
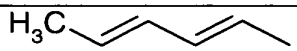
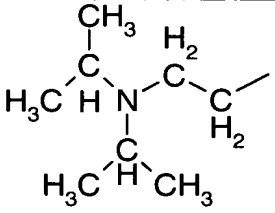
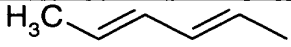
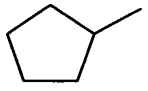
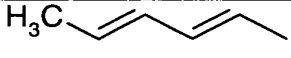
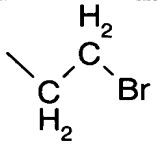


Table 4

Example	R1	R2	R3	UV_{max} (nm)	m/e	Yield (%)
243		H		504	(M+H) 554	97
244		H		500	(M+) 582	96
245		H		500	(M+H) 568	70
246		H		504	(M+H) 597	36
247		Br		504	(M+) 632/63	71

					4	
248		H		500	(M+H) 566	91
249		H		499	(M+) 569	52
250		H		504	(M+H) 616	99
251		H		500	(M+) 580	99
252		H		499	(M+H) 622	20
253		H		500	(M+H) 669	99
254		H		504	(M+H) 653	48
255		H		504	(M+H) 594	50
256		H		499	(M+H) 632/634	99

Exchange of the methoxy group at the F ring

The exchange of the methoxy groups at the F ring of the fredericamycin and at the derivatives is possible by primary, secondary or aromatic amines. Thereby, the components are stirred with the appropriate primary or secondary amines at room temperature in DMF or in another inert solvent. With aromatic amines, a catalysis with Lewis acids such as stannous(IV)chloride, etc. is required.

Diagram 11

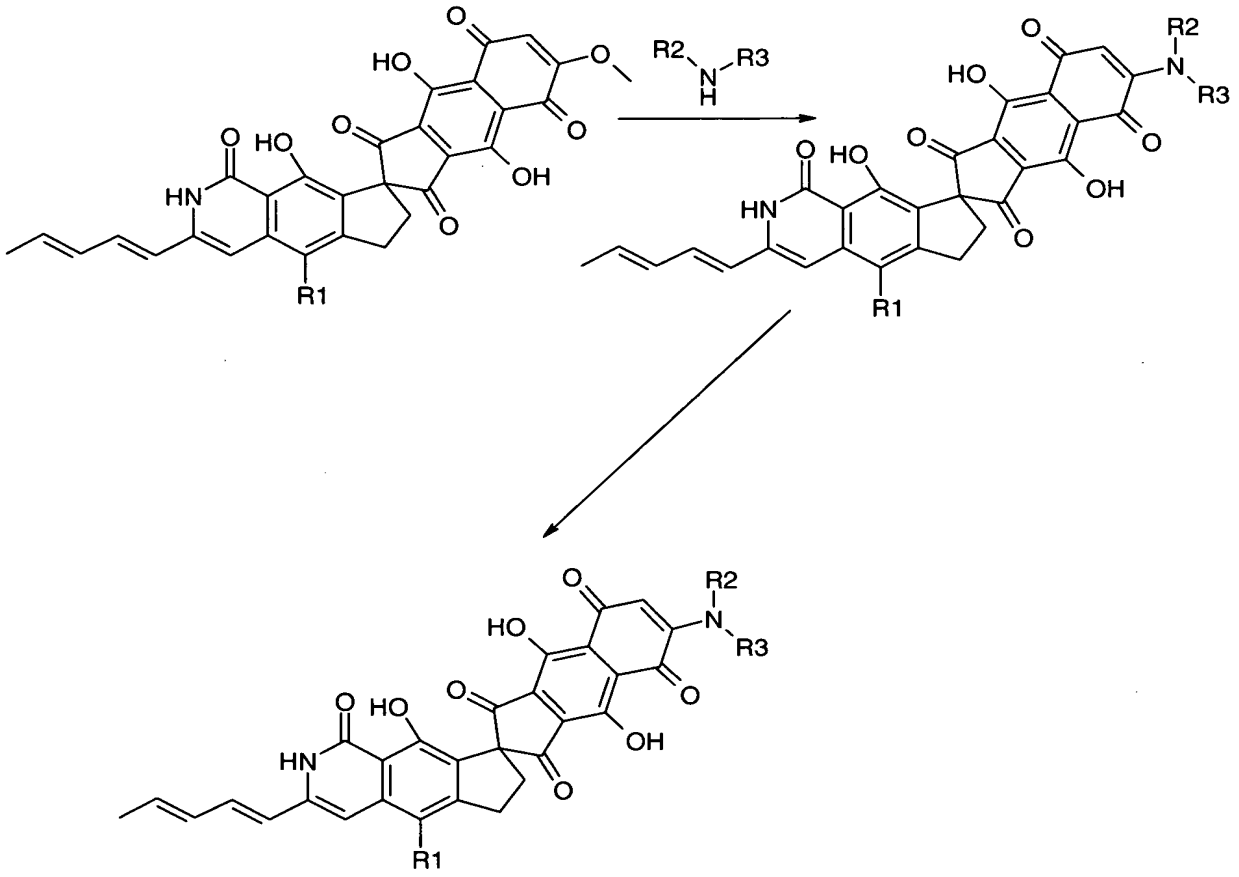
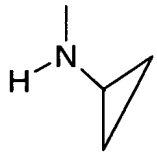
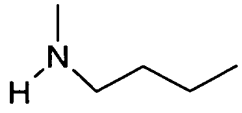
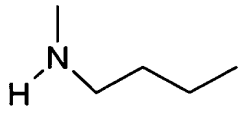
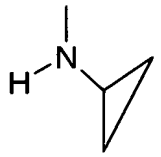
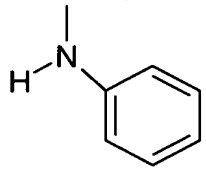
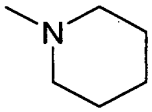
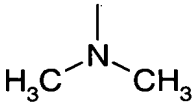
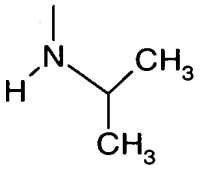
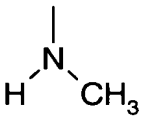
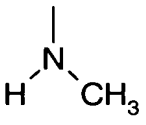
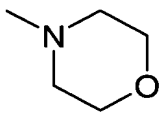
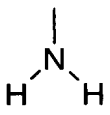
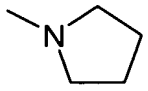
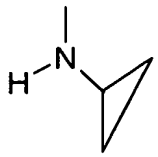


Table 5

R1	R2, N, R3	Example
I		257
I		258

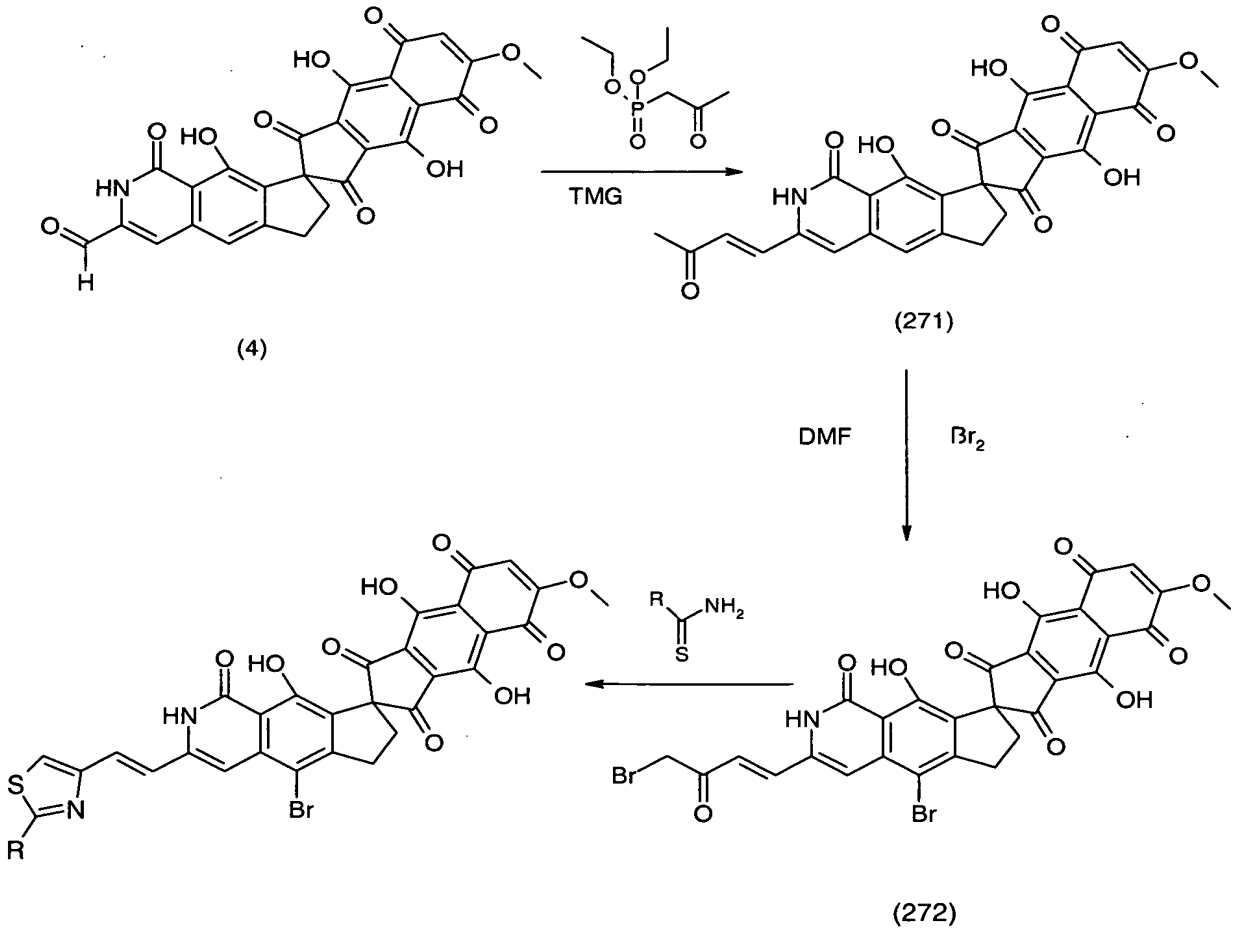
Br		259
H		260
H		261
H		262
H		263
H		264
H		265
I		266
H		267
H		268
H		269

Br		270

Preparation of heterocyclic fredericamycin derivatives

The fredericamycin aldehyde (4) can be reacted to pyridal acetone (271) according to Wittig or Wittig-Horner. Bromation with bromine in DMF yields the dibromo-derivative (272) substituted in the side chain and at the B ring. With the appropriately substituted thioamides or thioureas, the respective thiazole derivatives (273-276) are accessible.

Diagram 12



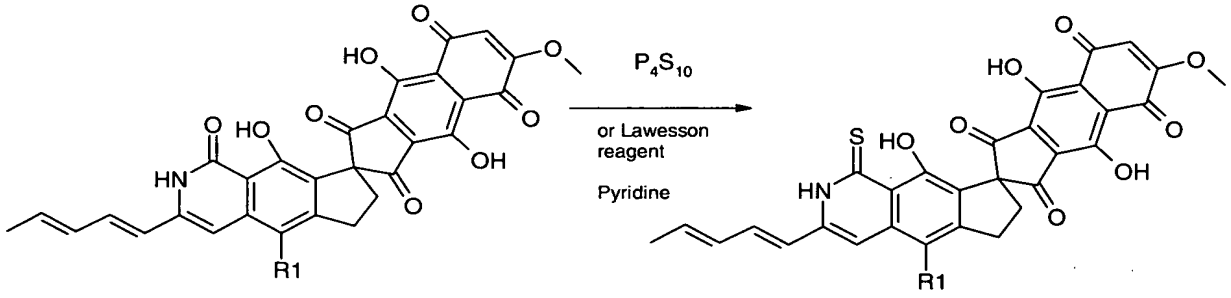
TMG: Tetramethylguanidine

Table 6

R	Example
NH_2	273
Ph	274
CH_3CONH	275
CH_3	276

Preparation of thioanalogoues of fredericamycin derivatives

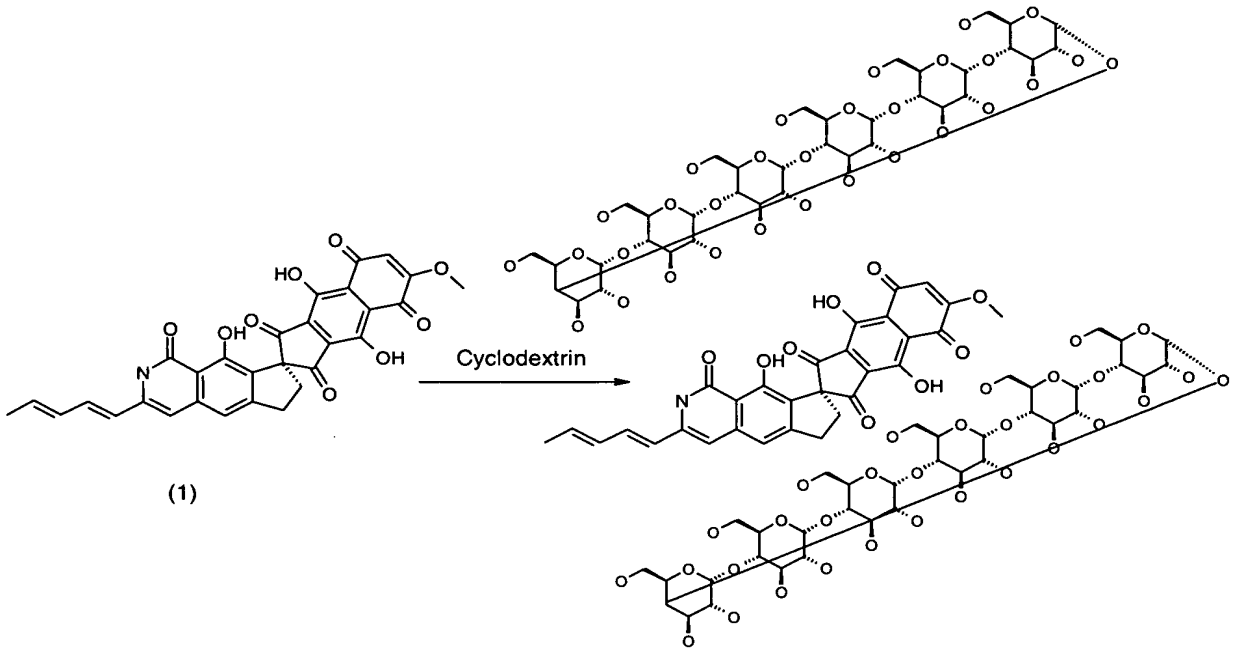
By sulfurization of fredericamycin or its derivatives with Lawesson reagent or P_4S_{10} in pyridine, the derivatives analogous to thiopyridone are accessible (see diagram 13).



R1: H, (277)

Fredericamycin (1) forms inclusion compounds such as (25) with polysugars such as α-cyclodextrin, that have good water solubility compared to the original substance.

The dextrin inclusion compounds form easily if the components are mixed in the appropriate stoichiometric ratio in a suitable solvent such as DMSO (see diagram 11).



(1)

(22)

Biological activity against 12 cancer cell lines:

LCL (H460, lung), MACL (MCF7, breast), LXFL (52L, lung), LXFA (629L, lung), MEXF (462NL, melanoma), MEXF (514L, melanoma), MAXF (401NL, breast), RXF (944L, renal), RXF (486L, renal), UXF (1138L, uterus), PRXF (PC3M, prostate), PRXF (22RV1).

Efficacy (IC70) averaged over all cell lines in µg/mL at 5 test concentrations

Table 7

Example / reference	**IC70 µg/mL**
adriamycin	**0.0210**
cisplatin	**37.1020**
fredericamycin	**0.2790**
1	0.1130
13	0.0050
14	0.0070
22	0.0080
23	0.0110
121	0.2020
127	0.1550
192	0.0750
196	0.0950

197	0.0340
198	0.2560
203	0.1590
212	0.2100
214	0.0220
215	0.0720
217	0.1290
218	0.0760
224	0.0470
225	0.1110
230	0.0910
232	0.3170
233	0.1000
234	0.0520
235	0.0810
236	0.1210
265	0.1330
275	0.3680
276	0.0840

Examples

Example 1

1-Desoxy-5-C-[(8R)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-yl]pentitol (2)

Two hundred (200) mg (0.38 mmol) fredericamycin A (1) are dissolved in 30 mL dichloromethane. After addition of 20 mL methanol and 4.4 ml water, 350 mg (2.6 mmol) N-methylmorpholine-N-oxide are added. Under vigorous stirring, 0.2 ml of a 2.5% osmium(IV)oxide solution in t-butanol is added dropwise. The reaction mixture is acidified with 2-3 drops of trifluoracetic acid. After stirring for 48 hours, the reaction is complete according to HPLC control (RP18, acetonitrile water (0.2% acetic acid)). The reaction mixture is added to 400 ml water under vigorous stirring, and the dark red crystalline solid is

sucked off through a filter. Drying in HV. Yield: 195 mg (87% of the theoretical value) dark red powder. ES^-: M/e = 606.2 (M+-H), λmax: 504.0.

Example 2

Tri-potassium-1-desoxy-5-C-[(8R)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-yl]pentitol (3)

Twelve (12.0) mg (19.8 µmol) fredericamycin tetrol (2) are dissolved in 1.5 mL absolute pyridine under nitrogen atmosphere. The solution is gassed for 30 min with argon at 0° C. Under the argon atmosphere, 5.94 mL of a 0.01 N KOH solution are added at once at 0° C. The reaction solution immediately turns turquoise. The reaction mixture is stirred for another 1 hour, and subsequently is frozen and lyophilized. Yield: 13.2 mg (100% of the theoretical value); deep blue crystal mass.

Example 3

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-carbaldehyde (4)

1.) Fifty (50) mg (82.3 µmol) tetrahydroxy fredericamycin (tetrol (2)) are dissolved in 4 mL DMF. Under vigorous stirring, an aqueous sodium iodate solution (300 mg $NaIO_4$ in 1 mL water) is added dropwise within one hour. After 1 h stirring at room temperature, 2 drops of trifluoracetic acid are added. After stirring for another 30 min, the reaction solution is diluted with 3 ml DMF, and 150 mg $NaIO_4$ dissolved in 0.5 ml water are added.
After another hour, 100 mL water are added. The supernatant over the precipitate is sucked off, and dryed in HV. Dark red crystal powder. Yield: 41 mg (100 % of the theoretical value). M/e = 501.3, UV_{max}: 504.0 nm.

2.) One hundred and nine (109) mg (179 µmol) fredericamycin tetrol (2) are dissolved in 8 mL pyridine. 180 µL water are added. To the reaction mixture, 450 mg (1.08 mmol, 6 eq.) (polystryrylmethyl)trimethylammonium periodate resin are added. Then the mixture is stirred

for 12 h at RT. The resin is filtered off; washing and concentrating until dry. Dark red residue. Yield: 89.9 mg (100 % of the theoretical value). M/e = 501.3, UV_{max}: 504.0 nm.

Example 4

1-[2-Oxo-2-((2E)-2-{[(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-yl]methylene}ethyl]-dimethylamino trifluoroacetate (118)

Twenty (20) mg (39.9 µmol) fredericamycin aldehyde (4) are dissolved under argon in 1.5 mL absolute DMF. Addition of 9.1 mg (47.9 µmol, 1.2 eq.) acetylhydrazide dimethylammoniumchloride (Girard reagent D) and 20 mg polyvinylpyridine (2% DVB). The mixture is stirred for 2.5 h. Then, 27 mg (80 µmol, 2.0 eq.) aldehyde Wang resin (coating: 3.0 mmol/g) are added and stirred for another 1 h. Then, the resin is filtered, and washed 3x with DMF. Concentration in high vacuum. The residue is dissolved in 1 ml trifluoracetic acid, and concentrated after 10 min until dry.

Red solid; Yield: 28.5 mg (100%); ES^+: M/e = 601.3, UV_{max}: 504.0 nm.

Example 5

1-[2-Oxo-2-((2E)-2-{[(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-yl]methylene}hydrazino)-ethyl]pyridinium chloride (119)

Fifteen (15) mg (29.9 µmol) fredericamycin aldehyde (4) are dissolved in 3 mL DMF. At room temperature 7.5 mg (40.0 µmol) acethydrazinopyridinium chloride (Girard reagent P) dissolved in 75 µL water are added. The reaction mixture is stirred for 1.5 h at room temperature, and the course of the reaction is monitored by HPLC. When finished, acetic acid ethyl ester is added to the reaction mixture, until a precipitation occurs. After the crystallization is finished, the red solid is sucked off.

Yield: 9.1 mg (44% of the theoretical value). M/e = 635.2; λ_{max}: 486.0.

Example 6

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-carbaldehyde oxime (122)

Ten (10) mg (19.4 µmol) fredericamycin aldehyde (4) are dissolved in 2 mL DMF. After addition of 3.1 mg (44.6 µmol) hydroxylammonium chloride, 3.2 µl pyridine are added. Stirring for 2 h at room temperature. The reaction mixture is added to 50 ml water and extracted 3 times with ethyl acetate. After drying and concentration, a deep red amorphous crystal powder was left (HPLC clean).

Yield: 7.4 mg (72% of the theoretical value). ES^-: M/e = 516.1; λ_{max}: 500.0 nm.

Example 7

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-carbaldehyde-O-methyloxime (8)

Ten (10) mg (19.4 µmol) fredericamycin aldehyde (4) are dissolved in 2 mL DMF. After addition of 3.4 mg (40.7 µmol) O-methylhydroxylammonium chloride and 3.2 µl pyridine, the reaction mixture is stirred for 2 h at room temperature. Then, it is added to 100 ml water, and the supernatant is sucked off from the red precipitate (HPLC clean).

Yield: 7.6 mg (71% of the theoretical value). ES^+: M/e = 531.2; λ_{max}: 500.0.

Example 8

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-carbaldehyde-O-benzyloxime (9)

Ten (10) mg (19.4 µmol) fredericamycin aldehyde (4) are dissolved in 2 mL DMF. After addition of 6.4 mg (43.2 µmol) O-benzylhydroxylammonium chloride and 3.2 µl pyridine, the reaction mixture is stirred for 2 h at room temperature. Then, it is added to 50 ml water, and the supernatant is sucked off from the red precipitate (HPLC clean).

Yield: 6.8 mg (57% of the theoretical value). ES^+: M/e = 607.2; λ_{max}: 504.0 nm.

Example 9

1-O-({(1*E*)-[(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-yl]methylene}amino)-β-D-glucopyranose (10)

Two (2.0) mg (4.0 µmol) fredericamycin aldehyde (4) are dissolved in 150 µL DMF, and 0.86 mg (4.4 µmol) β-aminoxy-D-glucopyranose is added. The mixture is stirred for 24 h at room temperature, and 5 mg (15.0 µmol) aldehyde Wang resin (coating: 3.0 mmol/g) is added. After stirring for another 3 h, the resin is filtered off, washed with DMF, and the filtrate is concentrated in high vacuum until dry.

Yield: 2.7 mg (99% of the theoretical value). red powder; ES^-: M/e = 678.1; λ_{max}: 504.0 nm.

Example 10

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1',3',5',8'(2H)-pentone (11)

Thirty (30) mg (49.4 µmol) tetrahydroxy fredericamycin (2) were dissolved in 2 mL pyridine. Twenty (20) mg (93.0 µmol) sodium metaperiodate dissolved in 0.3 ml water are added. After stirring for 4 h, 10 mg (260 µmol) sodium borohydride are added. After 12 h, concentration until dry, and the residue is separated by preparative HPLC.

Yield: 2.6 mg (13% of the theoretical value) red powder. ES^-: M/e = 503.2; λ_{max}: 504.0 nm.

Example 11

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-carboxylic acid (12)

Fifteen (15) mg (29.9 µmol) fredericamycin aldehyde (4) are dissolved in 1 mL dichloromethane and 0.5 ml t-butanol. Addition of 250 µl 2,4-dimethylbutene. Under stirring

at room temperature, a solution of 6.0 mg (53.1 µmol) sodium chlorite (80%) and 5.1 mg sodium hydrogenphosphate in 250 µl water are added dropwise.
After 2.5 h, again a solution of 10.0 mg (88.5 µmol) sodium chlorite and 5 mg sodium dihydrogenphosphate in 200 µl water are added. After altogether 4 h, it is put on water, and extracted with ethyl acetate.
The raw mixture was purified by preparative HPLC (RP18, acetonitrile-water-acetic acid). Red amorphous powder.

Yield: 68.3 mg (53.5% of the theoretical value). E^-: M/e = 516.1; λ_{max}: 504.0 nm.

Example 12

Potassium(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-carboxylate (13)

6.9 mg (13.3 µmol) Fredericamycin carboxylic acid (12) are dissolved in 5 mL DMF under nitrogen. At room temperature and under oxygen exclusion and vigorous stirring, 1.27 mL (12.7 µmol) of an aqueous 0.01 N KOH solution is added dropwise. It is stirred for 15 minutes at room temperature, and concentrated in high vacuum until dry.

Yield: 7.40 mg (100% of the theoretical value). E^-: M/e = 516.1; λ_{max}: 504.0 nm.

Example 13

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1',3',5',8'(2H)-pentone (14)

Twenty (20) mg (37.1 µmol) fredericamycin (1) were dissolved in 250 µl DMF, and then 6. 3 mg (35.3 µmol) N-bromosuccinimide in 250 µl DMF were added within one hour at 0° C. The reaction was stirred in a slowly thawing ice bath over night. Then, the DMF is removed in high vacuum, and the residue is purified by preparative HPLC.

Yield: 7 mg (32% of the theoretical value) red crystal mass. M/e = 616.1/618.1; λ_{max}: 486.0 nm.

Example 14

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1',3',5',8'(2H)-pentone (15)

Eighty four (84) mg (158 µmol) fredericamycin (1) were dissolved in 1.0 µl DMF, and then 33.0 mg (150.0 µmol) N-iodosuccinimide in 500 µl DMF were added within one hour at 0° C. The reaction was stirred in a slowly thawing ice bath over night. Then, the DMF is removed in high vacuum, and the residue (120 mg (14) with a content of 80%) is purified by preparative HPLC (gradient CH_3CN 50-90% over 16 min.)

Yield: 18 mg (17% of the theoretical value) red crystal mass. M/e = 665.0; λ_{max}: 484.0 nm.

Example 15

Methyl-2-{[(benzyloxy)carbonyl]amino}-3-[(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-yl]acrylate (23)

Sixty six (66) mg (200 µmol) Z-α-phosphonoglycine trimethylester are dissolved under argon in 1 mL absolute pyridine, and 25 µL 1,1,3,3-tetramethylguanidine are added at 0° C. After 40 min. 20 mg (40 µmol) fredericamycin aldehyde (4) is added at 0° C. After 15 min. 20 ml 1 M acetic acid is added, and the mixture is extracted 3 x with acetic acid. The raw product is purified by preparative HPLC (RP18, acetonitrile-water).

Yield: 10.0 mg (36% of the theoretical value). M/e = 706.4; λ_{max}: 492.0 nm.

Example 16

(8S)-9-hydroxy-4',6',9'-trimethoxy-2-methyl-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1',3',5',8'(2H)-pentone (24)

Ten (10) mg (15 µmol) fredericamycin (1) were dissolved under protective gas in 4 ml absolute DMF. At RT, 400 µl (4311 µmol) methyliodide and 81 mg powdered potassium

carbonate are added. The reactions mixture is then stirred at RT for 20 h, and is then transferred onto water. Extraction with ethyl acetate, and purification of the residue by separating chromatography on chloroform/methanol 30/1.

Yield: 4 mg (37% of the theoretical value). Yellow residue. M/e = 582.3; λ_{max}: 368.0 nm.

Example 17

Fredericamycin A 1:2 complex with α-cyclodextrin (22)

Ten (10) mg fredericamycin (0.025 mMol) are added to a solution of 50 mg α-cyclodextrin (0.050 mMol) in 500 µl dimethylsulfoxide. The solution is then diluted with 5 ml water. A stock solution prepared in such way can be diluted as desired with water.

λ_{max} = 504.0 nm.

Example 18

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-carbaldehyde(4-methylpiperazine-1-yl)hydrazone (111)

Five (5) mg (9.42 µmol) fredericamycin aldehyde (4) are dissolved in 500 µl DMF and 25 µl trifluoracetic acid. At room temperature, 1.30 mg (11.3 µmol) 1-amino-4-methyl-piperazine is added. After stirring for 4.5 h at room temperature, 1 equivalent each of Wang aldehyde resin and sulfonohydrazide resin is added and stirred for 2 h.
Filtration and concentration of the reaction solution at high vacuum.

Red powder. Yield: 5.4 mg (91% of the theoretical value). M/e = 599 $(M+H)^+$; λ_{max}: 504.0 nm.

Example 19

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-3-carbaldehyde-4,5-dihydro-1*H*-imidazole-2-yl-hydrazone (123)

Five (5.00) mg (9.42 µmol) fredericamycin aldehyde (4) are dissolved in 500 µl DMF and 25 µl trifluoracetic acid. At room temperature, 2.05 mg (11.3 µmol) 2-hydrazino-2-imidazolin hydrobromide is added. After stirring for 4.5 h at room temperature, 1 equivalent each of Wang aldehyde resin and sulfonohydrazide resin are added and stirred for 2 h.
Separation of the resin by filtration and concentration of the reaction solution at high vacuum.

Red powder. Yield: 3.9 mg (67% of the theoretical value). M/e = 584 $(M+H)^+$; λ_{max}: 504.0 nm.

Example 20

4',9,9'-Trihydroxy-6'-methoxy-3-{(*E*)-[(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)imino]methyl}-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2*H*)-pentone (123)

Five (5.00) mg (9.42 µmol) fredericamycin aldehyde (4) are dissolved in 500 µl DMF and 25 µl trifluoracetic acid. At room temperature, 1.67 mg (11.3 µmol) 2N-aminorhodanide are added. After stirring for 4.5 h at room temperature, 1 equivalent each of Wang aldehyde resin and sulfonohydrazide resin are added and stirred for 2 h.
Filtration and concentration of the reaction solution.

Red powder. Yield: 4.1 mg (65% of the theoretical value). M/e = 599 $(M+H)^+$; λ_{max}: 504.0 nm.

Example 21

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-*O*-(2-morpholine-4-ylethyl)oxime (27)

Five (5.00) mg (9.42 µmol) fredericamycin aldehyde (4) are dissolved in 500 µl DMF and 25 µl trifluoracetic acid. At room temperature, 2.47 mg (11.3 µmol) N-(aminoxyethyl)morpholine dihydrochloride is added. After stirring for 4.5 h at room temperature, 1 equivalent of Wang aldehyde resin (3.1 mg, 9.4 µmol, coating: 3.0 mmol/g) as well as 1 equivalent sulfonohydrazide resin (6.1 mg, 9.4 mmol, 1.5 mmol) are added and stirred for 2 h.

Filtration and concentration of the reaction solution.

Red powder. Yield: 6.1 mg (98% of the theoretical value). M/e = 630 $(M+H)^+$; λ_{max}: 504.0 nm.

Example 22

(8S)-5-chloro-4',6',9'-trimethoxy-2-methoxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1',3',5',8'(2H)-pentone (34)

Three hundred (300) mg (556.6 µmol) fredericamycin (1) are dissolved under argon in 10 µl DMF, and then 75.0 mg (556.6 µmol) N-chlorosuccinimide are added. The reaction is stirred for 5 h at 40° C. The reaction mixture is then added to 400 ml methanol/water 1:1, and the red precipitate is sucked off and dried at high vacuum.

Yield: 305 mg (96% of the theoretical value) red crystal mass. M/e = 573/575; λ_{max}: 504.0 nm.

Example 23

(8S)-5-fluoro-4',9,9'-trihydroxy-6'-methoxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2*H*)-pentone (35)

Fifty (50) mg (92.8 µmol) fredericamycin (1) are dissolved in 5 ml DMF under argon, and then 33.0 mg (93.5 µmol) 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) Selectfluor ® is added. The reaction is stirred for 24 h at room temperature. The reaction mixture is then added to 200 ml water, and is extracted with ethyl acetate. The concentrated raw product is purified by preparative HPLC (RP18, acetonitrile-water-acetic acid).

Yield: 7.1 mg (14% of the theoretical value) red crystal mass. M/e = 557; λ_{max}: 504.0 nm.

Example 24

1-Desoxy-5-C-[(8R)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl]-pentitol (36)

Hundred twenty (120) mg (209 mmol) chlorofredericamycin (34) are dissolved in 25.0 ml dichloromethane. After addition of 3.6 ml methanol and 0.8 ml water, 197 mg (1.46 mmol) N-methylmorpholine-N-oxide is added. Under vigorous stirring, 0.12 ml of a 2.5% solution of osmium(IV)oxide in t-butanol is added dropwise. After stirring for 27 hours, the reaction is complete, according to HPLC monitoring (RP18, acetonitrile-water (0.2% acetic acid)). The reaction mixture is added to 200 ml water under vigorous stirring, and the dark red solid is sucked off. Drying in HV.

Yield: 101 mg (75% of the theoretical value) dark red powder. M/e = 641/643; λ_{max}: 504.0.

Example 25

(8S)-4',9,9'-trihydroxy-5-bromo-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde (37)

Hundred (100) mg (200 µmol) fredericamycin aldehyde (4) are dissolved under argon in 5 ml DMF. Then, 200 µl of a 1M bromine solution in DMF is added. After stirring for 1.5 h at RT, another 20 µl bromine solution are added. According to HPLC monitoring, the reaction mixture is complete after 3.5 h.
Add to 150 ml water, and shake out with dichloromethane.

Yield: 96 mg (83% of the theoretical value) dark red powder. M/e = 579/581; λ_{max}: 504.0.

Example 26

1,2,3,4-Tetrahydro-5-bromo-4',9,9'-trihydroxy-6'-methoxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2*H*)-pentone (26)

Eight (8.0) mg (0.0128 mmol) 1,2,3,4-tetrahydrofredericamycin (25) are dissolved in 1 ml absolute DMF under nitrogen. Then a solution of 2.3 mg (0.0128 mmol) bromine in 0.25 ml

DMF is added dropwise to the solution. Stirring at room temperature over 24 h. The reaction mixture is concentrated to half volume in high vacuum, and is then transferred onto 100 ml water. The supernatant is sucked off from the precipitate and dried in a vacuum.

Red crystal powder 8.1 mg (88% of the theoretical value) m/e = 621/623; λ_{max}: 499 nm.

Example 27
(8S)-4',9,9'-trihydroxy-6'-benzylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2*H*)-pentone

Twenty (20) mg (37.1 µmol) fredericamycin are dissolved in 1 ml DMF under argon, then 4.76 mg (44.50 µmol) benzylamine are added at room temperature. According to HPLC (RP18, acetonitrile/water), a homogenous new product has formed after 3 h. The reaction mixture is concentrated at high vacuum until dry.

Red crystal mass; Yield: 23 mg (100% of the theoretical value) M/e = 615.3 (M+H); λ_{max}: 492 nm.

Example 28
(8S)-5-chloro-4',9,9'-trihydroxy-6'-benzylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2*H*)-pentone

Five (5.0) mg (8.71 µmol) 5-chlorofredericamycin are dissolved in 1 ml DMF under argon, then 1.12 mg (10.45 µmol) benzylamine are added at room temperature. After 29 h, the reaction mixture is concentrated at high vacuum until dry.

Red crystal mass; Yield: 5 mg (89% of the theoretical value) M/e = 649.1 (M+H); λ_{max}: 492 nm.

Example 28 (Translator: 28a)

(8S)-4',9,9'-trihydroxy-6'-ethanolamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2*H*)-pentone

Ten (10) mg (18.6 µmol) fredericamycin are dissolved in 1 ml DMF under argon, then 1.36 mg (22.3 µmol) ethanolamine are added at room temperature. According to HPLC (RP18, acetonitrile/water), a homogenous new product has formed after 3 h. The reaction mixture is concentrated at high vacuum until dry.

Red crystal mass; Yield: 9 mg (85% of the theoretical value) M/e = 569.3 (M+H); λ_{max}: 500 nm.

Example 29

(8S)-4',9,9'-trihydroxy-6'-(4-piperidylmethylamino)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2*H*)-pentone

Ten (10) mg (18.6 µmol) fredericamycin are dissolved in 1 ml DMF under argon, then 2.7 µl (22.3 µmol) 4-aminomethylpiperidine are added at room temperature. The reaction mixture is concentrated at high vacuum until dry after 24 h.

Red crystal mass; Yield: 11 mg (99% of the theoretical value) M/e = 622.3 (M+H); λ_{max}: 492 nm.

Examples 100 – 142

The compounds 100 – 142 can be generated analogously to examples 7, 8, 9, 10, 18, 19 and 20:

Example 100

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehydepyridine-2-yl-hydrazone (100)

Yield: (95% of the theoretical value) MS: M/e = 593.1; λ_{max}: 500.0 nm.

Example 101

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde [4-(trifluoromethyl)pyrimidine-2-yl]hydrazone (101)

Yield: (95% of the theoretical value) MS: M/e = 562.1; λ_{max}: 500.0 nm.

Example 102

N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]pyridyl-3-carbohydrazine (102)

Yield: (95% of the theoretical value) MS: M/e = 621.1; λ_{max}: 492.0 nm.

Example 103

N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]isonicotinohydrazine (103)

Yield: (95% of the theoretical value) MS: M/e = 621.1; λ_{max}: 500.0 nm.

Example 104

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-1,2,4-triazole-4-ylhydrazone (104)

Yield: (80% of the theoretical value) MS: M/e = 568.1; λ_{max}: 500.0 nm.

Example 105

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-4,5-dihydro-1H-imidazole-2ylhydrazone (105)

Yield: (95% of the theoretical value) MS: M/e = 584.1; λ_{max}: 492.0 nm.

Example 106

N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]-2-furohydrazine (106)

Yield: (95% of the theoretical value) MS: M/e = 610.0; λ_{max}: 492.0 nm.

Example 107

4-Amino-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]benzohydrazine (107)

Yield: (95% of the theoretical value) MS: M/e = 635.1; λ_{max}: 492.0 nm.

Example 108

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehydethiosemicarbazone (108)

Yield: (95% of the theoretical value) MS: M/e = 558.0; λ_{max}: 492.0 nm.

Example 109

N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]thiophene-2-carbohydrazine (109)

Yield: (95% of the theoretical value) MS: M/e = 626.0; λ_{max}: 492.0 nm.

Example 110

2-(1*H*-indole-3-yl)-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazine (110)

Yield: (95% of the theoretical value) MS: M/e = 673.1; λ_{max}: 492.0 nm.

Example 111

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde(4-methylpiperazine-1-yl)hydrazone (111)

Yield: (95% of the theoretical value) MS: M/e = 599.1; λ_{max}: 492.0 nm.

Example 112

2-Oxo-2-{(2E)-2-[(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]-hydrazino}acetamide (112)

Yield: (95% of the theoretical value) MS: M/e = 587.1; λ_{max}: 492.0 nm.

Example 113

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2H)-pentone (113)

Yield: (95% of the theoretical value) MS: M/e = 632.0; λ_{max}: 500.0 nm.

Example 114

{(2E)-2-[(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]-hydrazino}acetonitrile (114)

Yield: (95% of the theoretical value) MS: M/e = 583.1; λ_{max}: 492.0 nm.

Example 115

2-Amino-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]benzohydrazine (115)

Yield: (95% of the theoretical value) MS: M/e = 635.1; λ_{max}: 492.0 nm.

Example 116

4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[2-morpholine-4-yl-ethyl]oxime (116)

Yield: (85% of the theoretical value) MS: M/e = 630.1; λ_{max}: 492.0 nm.

Example 117

(2E)-2-[(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]hydrazinecarboximidamide (117)

Yield: (95% of the theoretical value) MS: M/e = 558.1; λ_{max}: 500.0 nm.

Example 118

2-(Dimethylamino)-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazine (118)

Yield: (85% of the theoretical value) MS: M/e = 601.1; λ_{max}: 492.0 nm.

Example 119

1-[2-Oxo-2-((2E)-2-{[(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene}hydrazino)ethyl]pyridinium chloride (119)

Yield: (85% of the theoretical value) MS: M/e = 635.1; λ_{max}: 492.0 nm.

Example 120

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-methyloxime (120)

Yield: (90% of the theoretical value) MS: M/e = 531.1; λ_{max}: 492.0 nm.

Example 121

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-benzyloxime (121)

Yield: (95% of the theoretical value) MS: M/e = 607.1; λ_{max}: 492.0 nm.

Example 122

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde oxime (122)

Yield: (95% of the theoretical value) MS: M/e = 517.1; λ_{max}: 482.0 nm.

Example 123

1-O-({(1E)-[(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene}amino)-β-D-glucopyranose (123)

Yield: (95% of the theoretical value) MS: M/e = 679.1; λ_{max}: 500.0 nm.

Example 124

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-phenylsemicarbazone (124)

Yield: (95% of the theoretical value) MS: M/e = 635.1; λ_{max}: 492.0 nm.

Example 125

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehydesemicarbazone (125)

Yield: (95% of the theoretical value) MS: M/e = 559.1; λ_{max}: 492.0 nm.

Example 126

2-Piperidino-4-yl-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (126)

Yield: (95% of the theoretical value) MS: M/e = 641.1; λ_{max}: 492.0 nm.

Example 127

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(3-chlorobenzyl)oxime (127)

Yield: (95% of the theoretical value) MS: M/e = 641.1; λ_{max}: 492.0 nm.

Example 128

N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]-(2-methyl-1,3-thiazole-4yl)carbohydrazide (128)

Yield: (95% of the theoretical value) MS: M/e = 641.1; λ_{max}: 492.0 nm.

Example 129

2-(1*H*-imidazole-1-yl)-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (129)

Yield: (90% of the theoretical value) MS: M/e = 624.1; λ_{max}: 500.0 nm.

Example 130

2-(Acetylamino)-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (130)

Yield: (95% of the theoretical value) MS: M/e = 615.1; λ_{max}: 492.0 nm.

Example 131

2-(4-Methylpiperazine-1-yl)-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (131)

Yield: (50% of the theoretical value) MS: M/e = 656.1; λ_{max}: 492.0 nm.

Example 132

2-Morpholine-4-yl-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (132)

Yield: (60% of the theoretical value) MS: M/e = 643.1; λ_{max}: 492.0 nm.

Example 133

2-(Methylamino)-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (133)

Yield: (70% of the theoretical value) MS: M/e = 587.1; λ_{max}: 492.0 nm.

Example 134

2-[Isopropyl(methyl)amino]-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (134)

Yield: (70% of the theoretical value) MS: M/e = 629.1; λ_{max}: 492.0 nm.

Example 135

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[2-(dimethylamino)ethyl]oxime (127)

Yield: (90% of the theoretical value) MS: M/e = 588.1; λ_{max}: 492.0 nm.

Example 136

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[3-(4-(3-chlorophenyl)-piperazine-1-yl)propyl]oxime (136)

Yield: (85% of the theoretical value) MS: M/e = 753.1; λ_{max}: 492.0 nm.

Example 137

4',9,9'-Trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[3-(dimethylamino)propyl]oxime (137)

Yield: (70% of the theoretical value) MS: M/e = 602.1; λ_{max}: 492.0 nm.

Example 138

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehydepyridine-2-yl-hydrazone (138)

Yield: (95% of the theoretical value) MS: M/e = 627.0; λ_{max}: 500.0 nm.

Example 139

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde [4-(trifluoromethyl)pyrimidine-2-yl]hydrazone (139)

Yield: (95% of the theoretical value) MS: M/e = 696.0; λ_{max}: 500.0 nm.

Example 140

(8S)-5-chloro-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]pyridyl-3-carbohydrazine (140)

Yield: (95% of the theoretical value) MS: M/e = 655.0; λ_{max}: 500.0 nm.

Example 141

(8S)-5-chloro-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]isonicotinohydrazide (141)

Yield: (95% of the theoretical value) MS: M/e = 655.0; λ_{max}: 500.0 nm.

Example 142

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-1,2,4-triazole-4-ylhydrazone (142)

Yield: (90% of the theoretical value) MS: M/e = 602.0; λ_{max}: 500.0 nm.

Example 143

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-4,5-dihydro-1H-imidazole-2-ylhydrazone (143)

Yield: (95% of the theoretical value) MS: M/e = 618.0; λ_{max}: 500.0 nm.

Example 144

(8S)-5-chloro-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]-2-furohydrazide (144)

Yield: (95% of the theoretical value) MS: M/e = 644.0; λ_{max}: 500.0 nm.

Example 145

(8S)-5-chloro-4-amino-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]-benzohydrazide (145)

Yield: (95% of the theoretical value) MS: M/e = 669.0; λ_{max}: 500.0 nm.

Example 146

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehydethiosemicarbazone (146)

Yield: (95% of the theoretical value) MS: M/e = 609.0; λ_{max}: 500.0 nm.

Example 147

(8S)-5-chloro-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]thiophene-2-carbohydrazide (147)

Yield: (95% of the theoretical value) MS: M/e = 660.0; λ_{max}: 500.0 nm.

Example 148

(8S)-5-chloro-2-(1*H*-indole-3-yl)-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (148)

Yield: (95% of the theoretical value) MS: M/e = 707.1; λ_{max}: 500.0 nm.

Example 149

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde(4-methylpiperazine-1-yl)hydrazone (149)

Yield: (95% of the theoretical value) MS: M/e = 633.1; λ_{max}: 500.0 nm.

Example 150

(8S)-5-chloro-2-oxo-2-{(2*E*)-2-[4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]hydrazino}acetamide (150)

Yield: (95% of the theoretical value) MS: M/e = 621.0; λ_{max}: 500.0 nm.

Example 151

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2H)-pentone (151)

Yield: (95% of the theoretical value) MS: M/e = 665.3; λ_{max}: 500.0 nm.

Example 152

(8S)-5-chloro-{(2*E*)-2-[4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]hydrazino}acetonitrile (152)

Yield: (95% of the theoretical value) MS: M/e = 617.1; λ_{max}: 500.0 nm.

Example 153

(8S)-5-chloro-2-amino-N'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]benzohydrazide (153)

Yield: (95% of the theoretical value) MS: M/e = 669.1; λ_{max}: 500.0 nm.

Example 154

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[2-morpholine-4-yl-ethyl)oxime (154)

Yield: (95% of the theoretical value) MS: M/e = 664.1; λ_{max}: 500.0 nm.

Example 155

(8S)-5-chloro-(2*E*)-2-[(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]hydrazinecarboximidamide (155)

Yield: (95% of the theoretical value) MS: M/e = 592.1; λ_{max}: 500.0 nm.

Example 156

(8S)-5-chloro-2-(dimethylamino)-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (156)

Yield: (95% of the theoretical value) MS: M/e = 635.1; λ_{max}: 500.0 nm.

Example 157

(8S)-5-chloro-1-[2-oxo-2-((2E)-2-{[(8S)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]hydrazino)ethyl]pyridinium chloride (157)

Yield: (95% of the theoretical value) MS: M/e = 669.1; λ_{max}: 500.0 nm.

Example 158

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-*O*-methyloxime (158)

Yield: (95% of the theoretical value) MS: M/e = 565.0; λ_{max}: 500.0 nm.

Example 159

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-*O*-benzyloxime (159)

Yield: (95% of the theoretical value) MS: M/e = 641.1; λ_{max}: 500.0 nm.

Example 160

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde oxime (160)

Yield: (95% of the theoretical value) MS: M/e = 551.1; λ_{max}: 500.0 nm.

Example 161

(8S)-5-chloro-1-O-({(1E)-[(8S)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]amino)-β-D-glucopyranose (161)

Yield: (95% of the theoretical value) MS: M/e = 713.1; λ_{max}: 500.0 nm.

Example 162

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-phenylsemicarbazone (162)

Yield: (95% of the theoretical value) MS: M/e = 669.1; λ_{max}: 500.0 nm.

Example 163

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehydesemicarbazone (163)

Yield: (90% of the theoretical value) MS: M/e = 593.0; λ_{max}: 500.0 nm.

Example 164

(8S)-5-chloro-2-piperidino-4-yl-N'-[(1E)-[(8S)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (164)

Yield: (95% of the theoretical value) MS: M/e = 675.1; λ_{max}: 500.0 nm.

Example 165

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(3-chlorobenzyl)oxime (165)

Yield: (90% of the theoretical value) MS: M/e =675.0; λ_{max}: 500.0 nm.

Example 166

(8S)-5-chloro-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]a-2-methyl-1,3-thiazole-4yl-carbohydrazide (166)

Yield: (95% of the theoretical value) MS: M/e = 675.0; λ_{max}: 500.0 nm.

Example 167

(8S)-5-chloro-2-(1*H*-imidazole-1-yl)-N'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (1647)

Yield: (90% of the theoretical value) MS: M/e = 658.1; λ_{max}: 500.0 nm.

Example 168

(8S)-5-chloro-2-(acetylamino)-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (164)

Yield: (95% of the theoretical value) MS: M/e = 649.0; λ_{max}: 500.0 nm.

Example 169

(8S)-5-chloro-2-(4-methylpiperazine-1-yl)-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (169)

Yield: (60% of the theoretical value) MS: M/e = 690.1; λ_{max}: 500.0 nm.

Example 170

(8S)-5-chloro-2-morpholine-4-yl-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (170)

Yield: (60% of the theoretical value) MS: M/e = 677.1; λ_{max}: 500.0 nm.

Example 171

(8S)-5-chloro-2-(methylamino)-*N*'-[(1E)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (171)

Yield: (70% of the theoretical value) MS: M/e = 621.1; λ_{max}: 500.0 nm.

Example 172

(8S)-5-chloro-2-[isopropyl(methyl)amino]-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (172)

Yield: (95% of the theoretical value) MS: M/e = 675.1; λ_{max}: 500.0 nm.

Example 173

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[2-(dimethylamino)ethyl]-oxime (173)

Yield: (60% of the theoretical value) MS: M/e = 622.0; λ_{max}: 500.0 nm.

Example 174

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[3-(4-(3-chlorophenyl)-piperazine-1-yl)propyl]-oxime (174)

Yield: (90% of the theoretical value) MS: M/e = 787.1; λ_{max}: 500.0 nm.

Example 175

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[3-(dimethylamino)propyl]oxime (175)

Yield: (75% of the theoretical value) MS: M/e = 636.1; λ_{max}: 500.0 nm.

Example 176

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehydepyridine-2-yl-hydrazone (176)

Yield: (95% of the theoretical value) MS: M/e = 670.9; λ_{max}: 500.0 nm.

Example 177

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde [4-(trifluoromethyl)pyrimidine-2-yl]hydrazone (177)

Yield: (95% of the theoretical value) MS: M/e = 739.9; λ_{max}: 500.0 nm.

Example 178

(8S)-5-bromo-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]pyridyl-3-carbohydrazide (178)

Yield: (90% of the theoretical value) MS: M/e = 699.0; λ_{max}: 500.0 nm.

Example 179

(8S)-5-bromo-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]isonicotinohydrazide (179)

Yield: (90% of the theoretical value) MS: M/e = 699.0; λ_{max}: 500.0 nm.

Example 180

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-1,2,4-triazole-4-ylhydrazone (180)

Yield: (70% of the theoretical value) MS: M/e = 645.9; λ_{max}: 492.0 nm.

Example 181

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-4,5-dihydro-1H-imidazole-2-ylhydrazone (181)

Yield: (95% of the theoretical value) MS: M/e = 662.0; λ_{max}: 492.0 nm.

Example 182

(8S)-5-bromo-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]-2-furohydrazide (182)

Yield: (95% of the theoretical value) MS: M/e = 688.9; λ_{max}: 492.0 nm.

Example 183

(8S)-5-bromo-4-amino-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]benzohydrazide (183)

Yield: (95% of the theoretical value) MS: M/e = 713.0; λ_{max}: 500.0 nm.

Example 184

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehydethiosemicarbazone (184)

Yield: (95% of the theoretical value) MS: M/e = 653.0; λ_{max}: 500.0 nm.

Example 185

(8S)-5-bromo-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]thiophene-2-carbohydrazide (185)

Yield: (95% of the theoretical value) MS: M/e = 704.0; λ_{max}: 492.0 nm.

Example 186

(8S)-5-bromo-2-(1*H*-indole-3-yl)-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (186)

Yield: (95% of the theoretical value) MS: M/e = 751.1; λ_{max}: 500.0 nm.

Example 187

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde(4-methylpiperazine-1-yl)hydrazone (187)

Yield: (95% of the theoretical value) MS: M/e = 677.1; λ_{max}: 500.0 nm.

Example 188

(8S)-5-bromo-2-oxo-2-{(2*E*)-2-[(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]hydrazino}acetamide (188)

Yield: (95% of the theoretical value) MS: M/e = 665.0; λ_{max}: 500.0 nm.

Example 189

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1',3',5',8'(2H)-pentone (189)

Yield: (95% of the theoretical value) MS: M/e = 709.9; λ_{max}: 492.0 nm.

Example 190

(8S)-5-bromo-{(2*E*)-2-[(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]hydrazino}acetonitrile (190)

Yield: (95% of the theoretical value) MS: M/e = 661.0; λ_{max}: 500.0 nm.

Example 191

(8S)-5-bromo-2-amino-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]benzohydrazide (191)

Yield: (70% of the theoretical value) MS: M/e = 713.0; λ_{max}: 492.0 nm.

Example 192

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[2-morpholine-4-yl-ethyl)oxime (192)

Yield: (95% of the theoretical value) MS: M/e = 708.0; λ_{max}: 500.0 nm.

Example 193

(8S)-5-bromo-(2*E*)-2-[(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]hydrazinecarboximidamide (193)

Yield: (95% of the theoretical value) MS: M/e = 636.0; λ_{max}: 500.0 nm.

Example 194

(8S)-5-bromo-2-(dimethylamino)-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (194)

Yield: (95% of the theoretical value) MS: M/e = 679.0; λ_{max}: 500.0 nm.

Example 195

(8S)-5-bromo-1-[2-oxo-2-((2E)-2-{[(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene}hydrazino)ethyl]pyridinium chloride (195)

Yield: (95% of the theoretical value) MS: M/e = 713.0; λ_{max}: 500.0 nm.

Example 196

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-methyloxime (196)

Yield: (95% of the theoretical value) MS: M/e = 609.0; λ_{max}: 492.0 nm.

Example 197

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-*O*-benzyloxime (197)

Yield: (95% of the theoretical value) MS: M/e = 685.0; λ_{max}: 492.0 nm.

Example 198

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde oxime (198)

Yield: (95% of the theoretical value) MS: M/e = 595.0; λ_{max}: 492.0 nm.

Example 199

(8S)-5-bromo-1-O-({(1E)-[(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene}amino)-β-D-glucopyranose (199)

Yield: (90% of the theoretical value) MS: M/e = 757.0; λ_{max}: 500.0 nm.

Example 200

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde-phenylsemicarbazone (200)

Yield: (90% of the theoretical value) MS: M/e = 713.0; λ_{max}: 500.0 nm.

Example 201

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehydesemicarbazone (201)

Yield: (90% of the theoretical value) MS: M/e = 637.0; λ_{max}: 492.0 nm.

Example 202

(8S)-5-bromo-2-piperidino-4-yl-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (201)

Yield: (90% of the theoretical value) MS: M/e = 719.0; λ_{max}: 500.0 nm.

Example 203

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(3-chlorobenzyl)oxime (203)

Yield: (95% of the theoretical value) MS: M/e = 718.0; λ_{max}: 492.0 nm.

Example 204

(8S)-5-bromo-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]-2-methyl-1,3-thiazole-4yl-carbohydrazide (204)

Yield: (95% of the theoretical value) MS: M/e = 718.9; λ_{max}: 492.0 nm.

Example 205

(8S)-5-bromo-2-(1*H*-imidazole-1-yl)-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (205)

Yield: (95% of the theoretical value) MS: M/e = 702.0; λ_{max}: 500.0 nm.

Example 206

(8S)-5-bromo-2-(acetylamino)-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (206)

Yield: (95% of the theoretical value) MS: M/e = 693.0; λ_{max}: 492.0 nm.

Example 207

(8S)-5-bromo-2-(4-methylpiperazine-1-yl)-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (207)

Yield: (90% of the theoretical value) MS: M/e = 734.1; λ_{max}: 500.0 nm.

Example 208

(8S)-5-bromo-2-morpholine-4-yl-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (208)

Yield: (95% of the theoretical value) MS: M/e = 721.1; λ_{max}: 500.0 nm.

Example 209

(8S)-5-bromo-2-(methylamino)-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (209)

Yield: (95% of the theoretical value) MS: M/e = 665.0; λ_{max}: 500.0 nm.

Example 210

(8S)-5-bromo-2-[isopropyl(methyl)amino]-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (210)

Yield: (95% of the theoretical value) MS: M/e = 707.0; λ_{max}: 500.0 nm.

Example 211

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[2-(dimethylamino)ethyl]oxime (211)

Yield: (95% of the theoretical value) MS: M/e = 666.0; λ_{max}: 500.0 nm.

Example 212

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[3-(4-(3-chlorophenyl)-piperazine-1-yl)propyl]oxime (212)

Yield: (95% of the theoretical value) MS: M/e = 831.0; λ_{max}: 500.0 nm.

Example 213

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[3-(dimethylamino)propyl]oxime (213)

Yield: (95% of the theoretical value) MS: M/e = 680.0; λ_{max}: 492.0 nm.

Example 214

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-isopropyloxime (214)

Yield: (95% of the theoretical value) MS: M/e = 559.2; λ_{max}: 500.0 nm.

Example 215

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-n-hexyloxime (215)

Yield: (99% of the theoretical value) MS: M/e = 601.3; λ_{max}: 500.0 nm.

Example 216

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(4-fluorobenzyl)oxime (216)

Yield: (99% of the theoretical value) MS: M/e = 625.2; λ_{max}: 500.0 nm.

Example 217

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(4-chlorobenzyl)oxime (217)

Yield: (99% of the theoretical value) MS: M/e = 641.2; λ_{max}: 500.0 nm.

Example 218

(8S)-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(3-fluorobenzyl)oxime (218)

Yield: (99% of the theoretical value) MS: M/e = 625.3; λ_{max}: 500.0 nm.

Example 219

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-isopropyloxime (219)

Yield: (80% of the theoretical value) MS: M/e = 593.2; λ_{max}: 500.0 nm.

Example 220

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-n-hexyloxime (220)

Yield: (90% of the theoretical value) MS: M/e = 635.3; λ_{max}: 500.0 nm.

Example 221

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(4-fluorobenzyl)oxime (221)

Yield: (85% of the theoretical value) MS: M/e = 659.3; λ_{max}: 500.0 nm.

Example 222

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(4-chlorobenzyl)oxime (222)

Yield: (80% of the theoretical value) MS: M/e = 675.3; λ_{max}: 500.0 nm.

Example 223

(8S)-5-chloro-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(3-fluorobenzyl)oxime (223)

Yield: (80% of the theoretical value) MS: M/e = 659.3; λ_{max}: 500.0 nm.

Example 224

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-isopropyloxime (224)

Yield: (90% of the theoretical value) MS: M/e = 639.3; λ_{max}: 492.0 nm.

Example 225

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-n-hexyloxime (225)

Yield: (95% of the theoretical value) MS: M/e = 679.3; λ_{max}: 492.0 nm.

Example 226

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(4-fluorobenzyl)oxime (226)

Yield: (95% of the theoretical value) MS: M/e = 703.3; λ_{max}: 492.0 nm.

Example 227

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(4-chlorobenzyl)oxime (227)

Yield: (95% of the theoretical value) MS: M/e = 719.3; λ_{max}: 492.0 nm.

Example 228

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(3-fluorobenzyl)oxime (228)

Yield: (95% of the theoretical value) MS: M/e = 705.3; λ_{max}: 492.0 nm.

Example 229

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-isopropyloxime (229)

Yield: (99% of the theoretical value) MS: M/e = 685.3; λ_{max}: 500.0 nm.

Example 230

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-n-hexyloxime (230)

Yield: (99% of the theoretical value) MS: M/e = 727.4; λ_{max}: 500.0 nm.

Example 231

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(4-fluorobenzyl)oxime (231)

Yield: (99% of the theoretical value) MS: M/e = 751.3; λ_{max}: 500.0 nm.

Example 232

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(4-chlorobenzyl)oxime (232)

Yield: (99% of the theoretical value) MS: M/e = 767.3; λ_{max}: 500.0 nm.

Example 233

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(3-fluorobenzyl)oxime (233)

Yield: (99% of the theoretical value) MS: M/e = 751.3; λ_{max}: 500.0 nm.

Example 234

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-benzyloxime (234)

Yield: (99% of the theoretical value) MS: M/e = 733.3; λ_{max}: 500.0 nm.

Example 235

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[2-morpholine-4-yl-ethyl)oxime (235)

Yield: (99% of the theoretical value) MS: M/e = 756.3; λ_{max}: 500.0 nm.

Example 236

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-methyloxime (236)

Yield: (95% of the theoretical value) MS: M/e = 657.3; λ_{max}: 492.0 nm.

Example 237

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-(3-chlorobenzyl)oxime (237)

Yield: (99% of the theoretical value) MS: M/e = 767.3; λ_{max}: 492.0 nm.

Example 238

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde *O*-[3-(4-(3-chlorophenyl)-piperazine-1-yl)propyl]oxime (238)

Yield: (99% of the theoretical value) MS: M/e = 879.4; λ_{max}: 500.0 nm.

Example 239

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-carbaldehyde oxime (239)

Yield: (99% of the theoretical value) MS: M/e = 643.3; λ_{max}: 492.0 nm.

Example 240

(8S)-5-iodo-2-(4-methylpiperazine-1-yl)-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (240)

Yield: (99% of the theoretical value) MS: M/e = 782.3; λ_{max}: 500.0 nm.

Example 241

(8S)-5-iodo-2-morpholine-4-yl-*N*'-[(1*E*)-(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]acetohydrazide (241)

Yield: (99% of the theoretical value) MS: M/e = 782.3; λ_{max}: 500.0 nm.

Example 242

(8S)-5-iodo-2-oxo-2-{(2*E*)-2-[(4',9,9'-trihydroxy-6'-methoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl)methylene]hydrazino}acetamide (242)

Yield: (99% of the theoretical value) MS: M/e = 713.3; λ_{max}: 500.0 nm.

Example 243

(8S)-4',9,9'-trihydroxy-6'-ethoxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (243)

Five (5) mg (0.0095 mmol) fredericamycin (1) are suspended in 2.0 ml ethanol. Under N_2 atmosphere, 90 mg sodium acetate are added and boiled under reflux. After a few minutes, the suspension turns into a deep blue solution. After 24 h it is cooled, transferred onto water and shaken out with ethyl acetate (0.1% CF_3COOH). After drying and concentration, a chromatographically homogenous, red powder is left.

Yield: 5.0 mg (97% of the theoretical value) MS = 554 (M+H)+; λ_{max}: 504.0 nm.

Example 244

(8S)-4',9,9'-trihydroxy-6'-n-butoxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (244)

Six (6) mg (0.0114 mmol) fredericamycin (1) are suspended in 3.0 ml n-butanol. Under N_2 atmosphere, 50 mg potassium acetate are added and heated to 100° C. After a few minutes, the suspension turns into a deep blue solution. The solution is left for 1 h at this temperature, and is then cooled. It is transferred onto water and shaken out with ethyl acetate (0.1% CF_3COOH). After drying and concentration, a chromatographically homogenous red powder is left.

Yield: 6.2 mg (96% of the theoretical value) MS = 582 (M)+; λ_{max}: 500.0 nm.

Example 245

(8S)-4',9,9'-trihydroxy-6'-n-isopropyloxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (245)

Five (5) mg (0.0095 mmol) fredericamycin (1) are suspended in 3.0 ml n-propanol. Under N_2 atmosphere, 50 mg potassium acetate (anhydrous) are added and heated to 80° C. After a few minutes, the suspension turns into a deep blue solution. The solution is left for 48 h at this temperature, and is then cooled. It is transferred onto water and shaken out with ethyl acetate (0.1% CF_3COOH). After drying and concentration, a chromatographically homogenous red powder is left.

Yield: 3.7 mg (70% of the theoretical value) MS = 568 (M+H)+; λ_{max}: 500.0 nm.

Example 246

(8S)-4',9,9'-trihydroxy-6'-(2-dimethylaminoethoxy)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (246)

6.1 mg (0.01159 mmol) fredericamycin (1) are suspended in 3.5 ml N,N-Dimethylaminoethanol. Under N_2 atmosphere, 52 mg anhydrous potassium acetate are added and heated to 80° C. After a few minutes, the suspension turns into a deep blue solution. The solution is left for 1.5 h at this temperature, and is then cooled. It is transferred onto water and

shaken out with ethyl acetate (0.1% CF_3COOH). After drying and concentration, a chromatographically homogenous red powder is left.

Yield: 2.4 mg (36% of the theoretical value); MS = 597 (M+H)+; λ_{max}: 504.0 nm.

Example 247

(8S)-5-bromo-4',9,9'-trihydroxy-6'-(2-dimethylaminoethoxy)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (247)

Ten (10.0) mg (0.019 mmol) bromofredericamycin (14) are suspended in 3.0 ml ethanol. Under N_2 atmosphere, 50 mg anhydrous potassium acetate are added and heated to 80° C. After a few minutes, the suspension turns into a deep blue solution. The solution is left for 48 h at this temperature, and is then cooled. It is transferred onto water and shaken out with ethyl acetate (0.1% CF_3COOH). After drying and concentration, a chromatographically homogenous red powder is left.

Yield: 7.2 mg (71 % of the theoretical value); MS = 632/634 (M+H)+; λ_{max}: 504.0 nm.

Example 248

(8S)-4',9,9'-trihydroxy-6'-allyloxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (248)

9.6 mg (0.01824 mmol) fredericamycin (1) are suspended in 3.0 ml allyl alcohol. Under N_2 atmosphere, 58 mg anhydrous potassium acetate are added and heated to 70° C. After a few minutes, the suspension turns into a deep blue solution. The solution is left for 2.5 h at this temperature, and is then cooled. It is transferred onto water and shaken out with ethyl acetate (0.1% CF_3COOH). After drying and concentration, a chromatographically homogenous red powder is left.

Yield: 9.2 mg (91 % of the theoretical value); MS = 566 (M+H)+; λ_{max}: 500.0 nm.

The compounds 249, 250, 251, 252, 253, 254, 255 were generated analogously to the instructions 244-248:

Example 249

(8S)-4',9,9'-trihydroxy-6'-(2-hydroxyethoxy)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (249)

Yield: 5.2 mg (52 % of the theoretical value); MS = 569 (M)+; λ_{max}: 499.0 nm.

Example 250

(8S)-4',9,9'-trihydroxy-6'-benzyloxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (250)

Yield:10.2 mg (99 % of the theoretical value); MS = 616 (M+H)+; λ_{max}: 504.0 nm.

Example 251

(8S)-4',9,9'-trihydroxy-6'-cyclopropylmethoxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (251)

Yield: 12.9 mg (99 % of the theoretical value); MS = 580 (M)+; λ_{max}: 500.0 nm.

Example 252

1-Desoxy-5-C-[(8R)-4',9,9'-trihydroxy-6'-ethoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6',7',8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl]pentitol (252)

Yield: 2.0 mg (20 % of the theoretical value); MS = 622 (M+H)+; λ_{max}: 499.0 nm.

Example 253

(8S)-4',9,9'-trihydroxy-6'-(2-t-butoxycarbonylaminoethoxy)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (253)

Yield: 12.9 mg (99 % of the theoretical value); MS = 669 (M)+; λ_{max}: 500.0 nm.

Example 254

(8S)-4',9,9'-trihydroxy-6'-(2-N,N-diisopropylaminoethoxy)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (249)

Yield: 5.8 mg (48 % of the theoretical value); MS = 653 (M+H)+; λ_{max}: 500.0 nm.

Example 255

1-Desoxy-5-C-[(8R)-4',9,9'-trihydroxy-6'-ethoxy-1,1',3',5',8'-pentaoxo-1,1',2,3',5',6,7,8'-octahydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl]pentitol (255)

Yield: 5.5 mg (50 % of the theoretical value); MS = 594 (M+H)+; λ_{max}: 500.0 nm.

Example 256

(8S)-4',9,9'-trihydroxy-6'-(2-bromoethoxy)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (256)

10.6 mg (0.02014 mmol) fredericamycin (1) are suspended in 2.0 ml bromoethanol. Under N_2 atmosphere, 150 mg anhydrous potassium acetate are added and heated to 120° C. After a few minutes, the suspension turns into a deep blue solution. After 12 hours, addition of another 150 mg potassium acetate. The solution is left for another 12 h at this temperature, and is then cooled. It is transferred onto water and shaken out with ethyl acetate (0.1% CF_3COOH). After drying and concentration, a chromatographically homogenous red powder is left.

Yield: 11.5 mg (99 % of the theoretical value); MS = 632/634 (M+H)+; λ_{max}: 499.0 nm.

Example 257

(8S)-5-iodo-4',9,9'-trihydroxy-6'-cyclopropylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (257)

Five (5.0) mg (7.5 µmol) 5-iodofredericamycin (15) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 0.64 mg (11.2 µmmol) cyclopropylamine, it is stirred at room temperature for 3 h. Excess cycloprolylamine and DMF are removed at high vacuum. After drying and concentration, a chromatographically homogenous red powder is left.

Yield: 5.1 mg (99 %); MS = 691.3 (M+H)+; λ_{max}: 504.0 nm.

Example 258

(8S)-5-iodo-4',9,9'-trihydroxy-6'-n-butylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (258)

Five (5.0) mg (7.5 µmol) 5-iodofredericamycin (15) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 0.82 mg (11.2 µmmol) n-butylamine, it is stirred at room temperature for 20 h. Excess n-butylamine and DMF are removed at high vacuum. After drying and concentration, a chromatographically homogenous red powder is left.
Yield: 5.3 mg (99 %); MS = 707.3 (M+H)+; λ_{max}: 504.0 nm.

Example 259

(8S)-5-bromo-4',9,9'-trihydroxy-6'-n-butylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (259)

Five (5.0) mg (8.1 µmol) 5-bromofredericamycin (15) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 0.89 mg (12.2 µmmol) n-butylamine, it is stirred at room temperature for 20 h. Excess n-butylamine and DMF are removed at high vacuum. After drying and concentration, a chromatographically homogenous red powder is left.
Yield: 5.3 mg (99 %); MS = 659.4/661.4 (M+H)+; λ_{max}: 504.0 nm.

Example 260

(8S)-4',9,9'-trihydroxy-6'-cyclopropylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (260)

Five (5.0) mg (9.3 µmol) fredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 2.12 mg (37.2 µmmol) cyclopropylamine, it is stirred at room temperature for 2 h. Excess cyclopropylamine and DMF are removed at high vacuum. After drying and concentration, a chromatographically homogenous red powder is left.
Yield: 5.1 mg (99 %); MS = 565.4 (M+H)+; λ_{max}: 510.0 nm.

Example 261

(8S)-4',9,9'-trihydroxy-6'-anilino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (261)

Five (5.0) mg (9.3 µmol) fredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 3.46 mg (37.2 µmmol) aniline and 37.2 µg stannous(IV)chloride (1.0 M in CH_2Cl_2), it is heated to 60° C. The reaction mixture is stirred for 24 h, and then excess diethanolaminomethyl polystyrene resin is added. Stir for 1 h. Exhaust off the resin and wash

with DMF. The organic phase is concentrated at high vacuum. A chromatographically homogenous red powder is left.

Yield: 5.5 mg (99 %); MS = 601.1 (M+H)+; λ_{max}: 504.0 nm.

Example 262

(8S)-4',9,9'-trihydroxy-6'-piperidino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (262)

Five (5.0) mg (9.3 µmol) fredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 3.16 mg (37.2 µmmol) piperidine, it is stirred for 22 h at room temperature. Excess amine and DMF are removed in high vacuum. A chromatographically homogenous red powder is left.

Yield: 5.5 mg (99 %); MS = 593.4 (M+H)+; λ_{max}: 504.0 nm.

Example 263

(8S)-4',9,9'-trihydroxy-6'-dimethylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (263)

Five (5.0) mg (9.3 µmol) fredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 1.67 mg (37.2 µmmol) dimethylamine (2M in MeOH), it is stirred for 4 h at room temperature. Excess amine and DMF are removed in high vacuum. A chromatographically homogenous red powder is left.

Yield: 5.5 mg (99 %); MS = 553.6 (M+H)+; λ_{max}: 526.0 nm.

Example 264

(8S)-4',9,9'-trihydroxy-6'-isopropylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (264)

Five (5.0) mg (9.3 µmol) fredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 2.19 mg (37.2 µmmol) isopropylamine, it is stirred for 4 h at room temperature. Excess amine and DMF are removed in high vacuum. A chromatographically homogenous red powder is left.

Yield: 5.2 mg (99 %); MS = 567.3 (M+H)+; λ_{max}: 504.0 nm.

Example 265

(8S)-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (265)

Five (5.0) mg (9.3 µmol) fredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 0.34 mg (11.1 µmmol) methylamine (2M in CH_3OH), it is stirred for 19 h at room temperature. Excess amine and DMF are removed in high vacuum. A chromatographically homogenous red powder is left.

Yield: 5.0 mg (99 %); MS = 539.2 (M+H)+; λ_{max}: 504.0 nm.

Example 266

(8S)-5-iodo-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (266)

Five (5.0) mg (7.5 µmol) 5-iodofredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 0.28 mg (9.0 µmmol) methylamine (2M in CH_3OH), it is stirred for 2 h at room temperature. Excess amine and DMF are removed in high vacuum. A chromatographically homogenous red powder is left.

Yield: 5.0 mg (99 %); MS = 665.2 (M+H)+; λ_{max}: 492.0 nm.

Example 267

(8S)-4',9,9'-trihydroxy-6'-morpholino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (267)

Five (5.0) mg (9.3 µmol) fredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 3.24 mg (37.2 µmmol) morpholine, it is stirred for 18 h at room temperature. Excess amine and DMF are removed in high vacuum. A chromatographically homogenous red powder is left.

Yield: 5.5 mg (99 %); MS = 595.5 (M+H)+; λ_{max}: 518.0 nm.

Example 268

(8S)-4',9,9'-trihydroxy-6'-amino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (268)

Five (5.0) mg (9.3 µmol) fredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 0.67 mg (37.2 µmmol) ammonia (2M in EtOH), it is stirred for 24 h at room temperature. Excess ammonia and DMF are removed in high vacuum. A chromatographically homogenous red powder is left.

Yield: 4.8 mg (99 %); MS = 525.4 (M+H)+; λ_{max}: 504.0 nm.

Example 269

(8S)-4',9,9'-trihydroxy-6'-pyrrolidino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (269)

Five (5.0) mg (9.3 µmol) fredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 0.99 mg (13.9 µmmol) pyrrolidine, it is stirred for 19 h at room temperature. Excess amine and DMF are removed in high vacuum. A chromatographically homogenous red powder is left.

Yield: 5.3 mg (99 %); MS = 579.2 (M+H)+; λ_{max}: 554.0 nm.

Example 270

(8S)-5-bromo-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1,1'-3',5',8'(2H)-pentone (270)

Five (5.0) mg (8.1 µmol) 5-bromofredericamycin (1) are dissolved under argon in 1.0 ml anhydrous DMF. After addition of 0.70 mg (12.2 µmmol) cyclopropylamine, it is stirred for 5 h at room temperature. Excess cyclopropylamine and DMF are removed in high vacuum. A chromatographically homogenous red powder is left.

Yield: 5.0 mg (99 %); MS = 643.4/645.4 (M+H)+; λ_{max}: 492.0 nm.

Example 271

2-[Acetyl]-3-[(8S)-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl]ethene (271)

79.5 mg (479 µmol) (2-oxo-propyl)-phosphonic acid dimethylester are dissolved under argon in 8 ml absolute pyridine, and 60.2 µl (479 µmol) 1,1,3,3-tetramethylguanidine are added at 0° C. After 5 minutes, 80.0 mg (159.7 µmol) fredericamycin aldehyde (4) is added at 0° C.

After 2 hours, 100 ml 1 M hydrochloric acid are added, and the supernatant is sucked off from the precipitate. Dry under high vacuum.

Yield: 60.0 mg (69 % of the theoretical value); M/e = 542.2; λ_{max}: 492.0 nm.

Example 272

2-[Bromoacetyl]-3-[(8S)-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl]ethene (272)

Fifty (50.0) mg (92.4 µmol) acetyl fredericamycin are dissolved under argon in 5 ml absolute DMF, and then 36.9 mg (231.1 µmol) bromine as a 1 M bromine solution in DMF are added under exclusion of light. It is stirred for 23 h under exclusion of light, and then 100 ml water are added. The precipitate is sucked off and dried under high vacuum.

Yield: 57.0 mg (87 % of the theoretical value) red powder; M/e = 697.9/699.9/701.9; M+; λ_{max}: 504.0 nm.

Example 273

2-[2-Amino-thiazole-4-yl]-3-[(8S)-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl]ethene (273)

Twenty (20.0) mg (28.7 µmol) bromoacetyl fredericamycin (273) are dissolved under argon in 4ml absolute DMF. At room temperature, first 3.3 mg (43.0 µmol) thiourea, and then 20 mg IR120 H+ are added. After 2 hours, it is filtered off the resin, and added to 50 ml water. The precipitate is dried under high vacuum. Red powder.

Yield: 18.0 mg (93 % of the theoretical value); M/e = 676.1/678.1; (M+H); λ_{max}: 492.0 nm.

Example 274

2-[2-Phenyl-thiazole-4-yl]-3-[(8S)-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl]ethene (274)

Five (5.0) mg (7.2 µmol) bromoacetyl fredericamycin (273) are dissolved under argon in 1 ml absolute DMF. At room temperature, first 1.5 mg (10.8 µmol) thiobenzamide, and then 5 mg IR120 H+ are added. After 3.5 h, addition of hydrazinosulfonyl resin, and stirring for 2 h. It is filtered off the resin, and added to 10 ml water. The precipitate is dried under high vacuum. Red powder.

Yield: 3.0 mg (57 % of the theoretical value); M/e = 737.2/739.2; (M+H); λ_{max}: 492.0 nm.

Example 275

2-[2-Acetylamino-thiazole-4-yl]-3-[(8S)-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl]ethene (275)

Five (5.0) mg (7.2 µmol) bromoacetyl fredericamycin (273) are dissolved under argon in 1 ml absolute DMF. At room temperature, first 1.3 mg (10.8 µmol) acetylthiourea, and then 5 mg IR120 H+ are added. After 22 h, addition of hydrazinosulfonyl resin, and stirring for 2 h. It is filtered off the resin, and added to 10 ml water. The precipitate is dried under high vacuum. Red powder.

Yield: 2.0 mg (39 % of the theoretical value); M/e = 718.3/720.4; (M+H); λ_{max}: 492.0 nm.

Example 276

2-[2-Methyl-thiazole-4-yl]-3-[(8S)-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-3-yl]ethene (276)

Five (5.0) mg (7.2 µmol) bromoacetyl fredericamycin (273) are dissolved under argon in 1 ml absolute DMF. At room temperature, first 0.81 mg (10.8 µmol) thioacetamide, and then 5 mg IR120 H+ are added. After 2 h, addition of hydrazinosulfonyl resin, and stirring for 2 h. It is filtered off the resin, and added to 10 ml water. The precipitate is dried at high vacuum. Red powder.

Yield: 3.0 mg (62 % of the theoretical value); M/e = 675.2/677.2; (M+H); λ_{max}: 492.0 nm.

Example 277

(8S)-4',9,9'-trihydroxy-6'-methylamino-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[*g*]isoquinoline-8,2'-cyclopenta[*b*]-naphthalene]-1-thio-,1'-3',5',8'(2H)-tetrone-thiofredericamycin (277)

Ten (10.0) mg (18.5 µmol) fredericamycin (1) are dissolved under argon in 2 ml absolute pyridine. After addition of 20.5 mg (92.5 mmol) phosphorous-V-sulfide, it is heated for 12 h to 60° C. Addition of another 20.5 mg (92.5 mmol) phosphorous-V-sulfide. According to HPLC (acetonitrile/water CF_3COOH), the reaction was complete after 1 h. It is transferred onto water and shaken out with ethyl acetate. Dry and concentrate. Purple-red powder.

Yield: 5.0 mg (49 % of the theoretical value); M/e = 55.7; (M+H); λ_{max}: 504.0 nm.

Example A

Water solubility of the fredericamycin derivatives

The water solubility of the various fredericamycin derivatives can be determined in a 0.9% NaCl solution with a pH of 7.

The compounds (22) and (3) dissolve very well. Compound (6) dissolves well, and compounds (2), (10), and (13) are soluble. Compounds (5), (7), (11) and (12) are sufficiently and markedly better soluble than fredericamycin (compound (1)).